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LUMINOUS™: Study to observe the effectiveness and safety of ranibizumab through individualized patient treatment and associated outcomes

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<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AMD</td>
<td>(wet) Age-related Macular Degeneration</td>
</tr>
<tr>
<td>APTC</td>
<td>Antiplatelet Trialists’ Collaboration</td>
</tr>
<tr>
<td>BCVA</td>
<td>Best Corrected Visual Acuity</td>
</tr>
<tr>
<td>CNV</td>
<td>Choroidal Neovascularization</td>
</tr>
<tr>
<td>CRA</td>
<td>Clinical Research Associate</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRT</td>
<td>Central Retinal Thickness</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>eCRF/pCRF</td>
<td>electronic Case Report Form /paper Case Report Form</td>
</tr>
<tr>
<td>DME</td>
<td>Diabetic Macular Edema</td>
</tr>
<tr>
<td>DS&amp;E</td>
<td>Drug Safety &amp; Epidemiology</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>Fab</td>
<td>Antibody Fragment</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practices</td>
</tr>
<tr>
<td>GPP</td>
<td>Good Pharmacoepidemiology Practices</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-Related Quality of Life</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journals Editors</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IOP</td>
<td>Intraocular Pressure</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ISPE</td>
<td>International Society of Pharmacoepidemiology</td>
</tr>
<tr>
<td>LSC</td>
<td>LUMINOUS™ Steering Committee</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
</tr>
<tr>
<td>mCNV</td>
<td>myopic Choroidal Neovascularization</td>
</tr>
<tr>
<td>NEI VFQ-25</td>
<td>National Eye Institute Visual Function Questionnaire 25</td>
</tr>
<tr>
<td>OCT</td>
<td>Optical Coherence Tomography</td>
</tr>
<tr>
<td>PRN</td>
<td>Pro re nata (as needed)</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient-Reported Outcome</td>
</tr>
<tr>
<td>PT</td>
<td>Preferred Term</td>
</tr>
<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>RPE</td>
<td>Retinal Pigment Epithelium</td>
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<tr>
<td>RVO</td>
<td>Retinal Vein Occlusion</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<tr>
<td>SOC</td>
<td>System Organ Class</td>
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<tr>
<td>VA</td>
<td>Visual Acuity</td>
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<tr>
<td>VEGF A</td>
<td>Vascular Endothelial Growth Factor A</td>
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<td>WHO</td>
<td>World Health Organization</td>
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# Glossary of terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Assessment</td>
<td>A procedure used to generate data collected by the study.</td>
</tr>
<tr>
<td>Enrollment</td>
<td>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)</td>
</tr>
<tr>
<td>Patient number</td>
<td>A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study</td>
</tr>
<tr>
<td>Premature patient withdrawal</td>
<td>Point/time when the patient exits from the study prior to the planned completion of all ranibizumab administration and assessments; at this time ranibizumab administration is discontinued and no further assessments are planned</td>
</tr>
<tr>
<td>Stop study participation</td>
<td>Point/time at which the patient came in for a final evaluation visit or when ranibizumab was discontinued whichever is later</td>
</tr>
<tr>
<td>Ranibizumab discontinuation</td>
<td>Point/time when patient permanently stops taking ranibizumab for any reason; may or may not also be the point/time of premature patient withdrawal</td>
</tr>
<tr>
<td>Ranibizumab treatment naïve patient</td>
<td>A patient who was not treated with ranibizumab prior to providing informed consent</td>
</tr>
<tr>
<td>Primary treated eye</td>
<td>The first eye treated during the study. If both eyes are treated at baseline, or if both eyes were pre-treated (none treated at baseline), the eye with the earliest diagnosis date will be considered the primary treated eye. If both eyes have the same diagnosis date, one of the two eyes will be chosen randomly as the primary treated eye</td>
</tr>
<tr>
<td>Variable</td>
<td>Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points</td>
</tr>
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</table>
Amendment 2

Amendment rationale

The main purpose of this amendment is to:

- Align the content of the Section 7 Safety monitoring with the EMA “Guideline on Good Pharmacovigilance Practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products” (EMA/873138/2011). The special scenario events were newly defined as AEs and the transmission of an infectious agent via a medicinal product was newly defined as an SAE. A requirement to transfer the non-serious AEs monthly to the Novartis safety database was implemented. The impact of these changes will be to collect more comprehensive safety data in the clinical and safety databases.

- Enable enrollment of patients who received ocular treatment with any VEGF inhibitor other than ranibizumab up to a month prior to enrollment (instead of up to 90 days prior to enrollment). This change in the exclusion criteria is implemented to more accurately reflect the wider choice of VEGF inhibitors now routinely available in clinical practice and how they are used. The impact on the safety and efficacy results of the study is anticipated to be minimal.

- Collect study participant’s smoking history to provide comprehensive medical history information and investigate the potential effect of smoking history on study drug response.

- Clarify that visual acuity is recommended to be captured for both eyes (better- and worse-seeing eye) at baseline and each time the NEI VFQ-25 questionnaire is administered to ensure that VFQ-25 data can be properly interpreted.

In addition, Amendment 2 incorporates multiple changes to the protocol language to include the latest information, improve clarity and formatting, accuracy and ensure better adherence to the protocol.

The case report form will be revised to accommodate the changes described in this amendment. The current informed consent remains valid and will not be revised.

The study is actively recruiting and approximately 20,000 patients have been enrolled to date.

Unless otherwise stated above, the changes proposed in this amendment will neither affect the study population nor the management of the patients in the study.

Changes to the protocol

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

Section 7 - Safety monitoring – New reporting requirements for adverse events were inserted to reflect the EMA “Guideline on Good Pharmacovigilance Practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products” (EMA/873138/2011). The special scenario events were newly defined as AEs and the transmission of an infectious agent via a medicinal product was newly defined as a SAE. A requirement to transfer the non-serious AEs monthly to the Novartis safety database was implemented.
Section 4.2 – Exclusion criteria – AN exclusion criterion was changed from “Ocular treatment with any VEGF inhibitor other than ranibizumab in the 90 days prior to study enrollment” to “Ocular treatment with any VEGF inhibitor other than ranibizumab in the month prior to study enrollment”.

These 2 major changes were also reflected in the section Protocol synopsis. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough red font for deletions and red underlined for insertions.

The changes described in this amended protocol require IRB/IEC approval prior to implementation or IRB/IEC notification as appropriate depending on local regulations.
Amendment 1

Amendment rationale

The main purposes of this amendment are to:

• Introduce pregnancy reporting to enable collection of these data in an observational setting as it is anticipated that enrolment of patients with visual impairment due to diabetic macular edema or retinal vein occlusion are younger than the wet age-related macular degeneration population and therefore of child-bearing potential.

• Add a baseline characteristics interim look when approximately 2000 patients are enrolled in the study to communicate the data on the patient population enrolled in LUMINOUS™.

• Remove the reference to combination of prospective data collection with patient data from previous local ranibizumab registries. This data migration will not be performed in this study.

• Remove the inclusion criterion “Willing and able to complete a brief self-reported questionnaire at pre-specified time points”. The National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) assessment is now optional.

In addition, Amendment 1 incorporates multiple changes to the protocol language to improve clarity, accuracy, ensure better adherence to the protocol and the collection of high quality data. The updated structure of the protocol amendment is in accordance with updated Novartis protocol standards.

The informed consent and the case report form will be revised to accommodate the changes described in this amendment.

The study is actively recruiting and approximately 800 patients have been enrolled to date.

The changes proposed in this amendment will not affect the study population or the management of the patients in the study.

Changes to the protocol

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

Study title: In order to facilitate compliance with the various local laws and regulations, Lucentis® is replaced by ranibizumab in the study title.

Protocol synopsis: The synopsis is revised to match the core protocol amendment.

Section 1 - Introduction: Information on the new ranibizumab indications approved, visual impairment due to diabetic macular edema and visual impairment due to retinal vein occlusion, are introduced.

Section 2 – Study objectives: The objectives are clarified and better specified in line with the unchanged goals of the study.

Section 3 – Investigational plan: This section is clarified and the introduction of the baseline characteristics interim look is described.
Section 4 – Population: The inclusion criterion on the NEI VFQ-25 questionnaire is removed to better reflect routine clinical practice.

Section 5 – Treatment: Additional sections are added to provide more clarity and further explanations on the protocol to the investigative sites.

Section 6 – Visit schedule, assessments and data collection: This section is revised to provide more precision on the data collected in the CRF, update the requirement for the NEI VFQ-25 questionnaire and correct few discrepancies.

Section 7 – Safety monitoring: This section is updated to ensure better adherence of the participating sites with safety reporting and pregnancy reporting is added.

Section 8 – Data review and database management: This section is clarified to better reflect the study procedures.

Section 9 – Data analysis: This section is updated to provide additional clarifications on the analyses planned during the study.

Section 10 – Ethical and regulatory considerations: This section is amended to further clarify the procedures for the study and correct discrepancies.

Changes will be implemented throughout the protocol. Besides, Novartis updated protocol standards have also been implemented throughout the protocol.

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

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation or IRB/IEC notification as appropriate depending on local regulations. In addition, the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol according to any relevant local regulations.
Protocol synopsis

Title of study: LUMINOUS™: Study to observe the effectiveness and safety of ranibizumab through individualized patient treatment and associated outcomes

Background and rationale: Ranibizumab (Lucentis®) – a recombinant, humanized, monoclonal antibody fragment (Fab) that neutralizes all active forms of vascular endothelial growth factor A (VEGF-A) – represents standard first line therapy for neovascular age-related macular degeneration (wet AMD).

Although the efficacy and safety of ranibizumab have been established in phase III clinical trials, long term safety and effectiveness in the real-world setting have not been widely documented in large populations across diverse regions. In addition, patient management practices that could potentially serve to improve individual treatment effectiveness in real world clinical practice have not yet been established. Finally, limited data exist describing Health Related Quality of Life (HRQoL) outcomes in patients treated with ranibizumab. Therefore, a five-year, non-randomized, observational, multicenter study will be conducted in selected countries where ranibizumab is marketed to further study and describe the long term safety and effectiveness, treatment patterns, and HRQoL associated with ranibizumab treatment for any approved indication included in the local product label.

Primary Objectives:
- To describe the safety for all approved indications included in the local product label as observed in this 5-year study duration and assessed by the type, frequency, severity and relationship of all systemic and ocular adverse events
- To describe the effectiveness of ranibizumab in routine clinical practice for all approved indications included in the local product label as observed in this 5-year study duration and assessed by mean change in visual acuity over time and mean change in CRT over time if data allow

Secondary objectives:
- To describe treatment patterns for ranibizumab in routine clinical practice for all approved indications included in the local product label as assessed by overall number of injections, number of visits, time interval between injections, duration of treatment period, number of re-treatment, reasons for re-treatment and reasons for treatment termination
- To assess the HRQoL of patients treated with ranibizumab in routine clinical practice for all approved indications included in the local product label as assessed by the change from baseline in NEI VFQ-25 composite and subscale scores

Population: This study will include consenting patients who have previously been treated with, who are currently being treated with, or are initiating treatment with ranibizumab for any approved indication included in the local product label.

Inclusion/Exclusion criteria:
Patients eligible for inclusion in this study must fulfill all of the following criteria:
- Adults patients, within age limit as defined by local regulations and local product label, who have previously been treated with, who are currently being treated with, or initiating treatment with ranibizumab for any approved indication included in the local product label; and
- Willing and able to provide informed written consent personally or by legal proxy

Patients fulfilling any of the following criteria are not eligible for inclusion in the study:
- Simultaneous participation in a study that includes administration of any investigational drug or procedure
- Systemic treatment with any VEGF inhibitor in the 90 days prior to enrollment
- Ocular treatment with any VEGF inhibitor other than ranibizumab in the month prior to enrollment
**Study design:** This study is designed as an observational, multicenter study in patients being treated with ranibizumab for any approved indication included in the local product label. This study does not direct therapy or recommend any treatment other than that patients be treated in accordance with the ranibizumab local product label. The duration of the study is anticipated to be 5 years, with a minimum of 1 year follow-up period per patient.

Patients will be recruited from outpatient ophthalmology clinics in selected countries where ranibizumab is marketed. Timing of actual patients visits is at the discretion of the investigator. If patients are not seen at least once per year, they will be discontinued from the study.

**Safety assessments:** All SAEs reported to or noted by the physician from the time the patient signs the informed consent until 30 days after study discontinuation will be recorded in the AE CRF and reported to Novartis. All AEs will be captured on the AE CRF throughout the safety recording period (see Section 7 for details). AEs detected through ophthalmic examinations will be collected if available.

**Clinical assessments and data collection:** Timing of actual patient visits is at the discretion of the treating physician.

All visits should be documented in the CRF. It is recommended that CRFs are completed after every visit and at a minimum of every 3 months post visit.

Data elements to be collected include demographics and medical history/ocular history (baseline only), relevant prior and concomitant medications, treatment information, VA, SAEs/AEs, and HRQoL using the NEI VFQ-25. The NEI VFQ-25 may be collected approximately once per year at the time of the clinic visit or at home.

Physicians will be encouraged to follow-up with patients who have not been seen in the clinic for at least 6 months since the last visit to capture any SAEs that may have occurred since the previous visit, and again 6 months later if no subsequent visit occurs within the following 6 months. If patients are not seen at least once per year, they will be discontinued from the study. Any SAEs experienced should be reported for 30 days after study discontinuation.

**Data analysis:**

The primary safety objective of this study will be assessed based on the incidence rate, relationship and severity of treatment emergent ocular and non-ocular adverse events during defined time periods (duration of 1 year to 4 years).

Non-ocular adverse events will be assessed for the safety set; ocular adverse events will be assessed for the primary treated eye set.

The primary efficacy variable will be the mean change in visual acuity (VA) at quarterly intervals from the baseline visit for the primary treated eye set.

Mean change in CRT over time by type of OCT machine (spectral domain or time domain) at quarterly intervals from the baseline visit will be summarized for primary treated eye set and for the secondary treated eye set. As CRT data are optional, this analysis will be performed only if data allow.

The number of ranibizumab treatments by patient and by primary treated eye will be summarized.
1 Introduction

1.1 Background

Ranibizumab (Lucentis®) – a vascular endothelial growth factor A (VEGF-A) inhibitor – represents standard first line therapy for neovascular age-related macular degeneration (wet AMD). Whereas previous treatments were effective in slowing the progression of disease and disability, ranibizumab has been shown not only to prevent vision loss but also to improve visual acuity (Rosenfeld et al., 2006; Brown et al., 2006; Ferrara et al., 2006; Morris et al., 2007; Maloney et al., 2007).

Although the efficacy and safety of ranibizumab have been established in phase III clinical trials (Rosenfeld et al., 2006; Brown et al., 2006; Brown et al., 2009; Mitchell et al. 2011; Campochiaro et al., 2010; Brown et al., 2010), long term safety and effectiveness in routine clinical practice have not been widely documented in large populations. Furthermore, treatment patterns and patient-reported health-related quality of life (HRQoL) as it relates to visual function have not been widely studied in the real-world setting. In order to address these questions, an observational, multicenter study in countries where ranibizumab is marketed to describe the long-term safety and effectiveness, treatment patterns and HRQoL in patients treated with ranibizumab for any approved indication included in the local product label, will be conducted.

1.1.1 Diseases

Neovascular (wet) age-related macular degeneration (AMD)

AMD causes severe vision loss and is the leading cause of blindness in individuals older than 50 years in the Western World (Friedman et al., 2004; Evans et al., 1996; Bressler NM., 2004; Resnikoff et al., 2004; Augood et al., 2004; Ferris et al., 1984; Klein et al., 1992).

The non-neovascular (“dry”) form of AMD is the most common type and accounts for 85% of all AMD cases. This non-exudative form is characterized by drusen and atrophic changes in the retinal pigment epithelium (RPE). The second and less common, exudative (“wet”) form of AMD is characterized by choroidal neovascularization (CNV). In CNV, the newly formed vessels have a tendency to leak blood and fluid, causing symptoms of scotoma and metamorphopsia. Furthermore, these new vessels are accompanied by proliferation of fibrous tissue (Green et al., 1993) leading to loss of photoreceptors within 3 to 24 months. The lesion can continue to grow, resulting in progressive, severe vision loss. Though the wet form of AMD is much less common, 80% to 90% of severe vision loss related to AMD is attributable to this form characterized by CNV (Bressler et al., 1988; de Jong PTVM., 2006).

Although the pathogenesis of AMD is not fully understood, there is evidence from preclinical data that VEGF-A, a diffusible cytokine that promotes angiogenesis and vascular permeability, plays a key role in the formation of CNV lesions.
Visual impairment due to diabetic macular edema (DME)

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 diabetes 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, mediating high-resolution vision (Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group, 1985) 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 et al., 1997; Vinores et al., 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 et al., 2009). Thus, inhibition of intravitreal VEGF with ranibizumab addresses a main cause of the pathology.

While laser photocoagulation is widely used in the management of DME, the treatment does not improve vision on average and still leaves 13% of subjects losing more than 15 letters of vision at the end of three years.

Visual impairment due to macular edema secondary to retinal vein occlusion (RVO)

Retinal vein occlusion (RVO) is the second most common retinal vascular permeability disorder after diabetic retinopathy and is a significant cause of visual handicap. Macular edema (ME) is the most common cause of vision loss in patients with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Macular edema is characterized by swelling of the central part of the retina that mediates high-resolution vision. When the area of swelling involves the foveal center, vision is likely to be impaired.

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

Visual impairment due to CNV secondary to pathologic myopia (mCNV)

CNV secondary to pathologic myopia (mCNV) is considered one of the major causes of legal blindness in several countries and the leading cause of visual impairment in younger patients worldwide (Ohno-Matsui et al, 2003; Yoshida et al, 2003; Cohen et al 1996).

The most commonly used definition of mCNV includes an abnormal elongation of the axial length of the eyeball (more than 26 mm) associated with high myopia (refractive errors greater than -6.0 Diopters [D]) and clinical characteristics mostly accompanied by anatomical changes of the posterior pole of the eye, such as posterior staphyloma, atrophy of the retinal pigment epithelium (RPE), Bruch’s membrane cracks, subretinal hemorrhage, retinal detachment and CNV, the most vision threatening considered complication in pathologic myopia (Miller et al, 2001; Pruett 1994).
The prevalence of mCNV is high in patients under the age of 50 years. Due to the occurrence of this pathology at a younger age, a profound impact on patients’ lives is expected, affecting the productivity of the working age group as well as the main financial resource of an entire family (Miller et al, 2006).

In the future, more retinal diseases could be indicated for treatment with ranibizumab. These diseases can be evaluated in this study, once approved in the local product label during the study period.

Therefore, once an indication is approved in a participating country, patients diagnosed with this indication can be eligible for inclusion in the study.

1.1.2 Ranibizumab

Ranibizumab is a recombinant, humanized monoclonal antibody fragment (Fab) that neutralizes all active forms of VEGF-A. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation (Lucentis® Summary of Products Characteristics).

Wet age-related macular degeneration (AMD)

Efficacy and safety of ranibizumab have been demonstrated in a number of major clinical trials such as MARINA (Rosenfeld et al., 2006), ANCHOR (Brown et al., 2006; Brown et al., 2009), PIER (Regillo et al., 2008; Abraham et al., 2010), EXCITE (Schmidt-Erfurth et al., 2010), SUSTAIN (Holz et al., 2011), CATT (Martin et al, 2012), HARBOR (Busbee et al, 2013) and IVAN (Chakravarthy, et al 2013).

Subsequent to the encouraging 1-year data from the ANCHOR and PIER trials and positive 2-year data from the MARINA trial, ranibizumab (Lucentis®) received approval for the treatment of all angiographic subtypes of CNV secondary to AMD from the United States Food and Drug Administration, European Medicines Agency (EMA), and Australian Therapeutic Goods Administration in June 2006, January 2007, and March 2007, respectively.

The pivotal MARINA and ANCHOR trials have shown that monthly intravitreal injections of ranibizumab not only maintain but also improve visual acuity (VA) and function in patients with neovascular AMD (Rosenfeld et al., 2006; Brown et al., 2006; Brown et al., 2009). In the PIER trial, quarterly treatment scheduling was better than sham treatment, but it did not maintain any visual improvement (Regillo et al., 2008; Abraham et al., 2010). The randomized, double-masked, active control, multicenter phase III trial EXCITE (Schmidt-Erfurth et al., 2010) where participants also received quarterly injections after three loading doses, showed improved vision but not to the level achieved by the monthly regimen. These trials found that intravitreal doses of ranibizumab given quarterly were clearly superior than treatment with sham (MARINA) or verteporfin photodynamic therapy (ANCHOR) in patients with CNV secondary to AMD but were unable to deliver the same improvement in vision as the monthly treatment.
Results from the Prospective OCT Imaging of Patients with Neovascular AMD Treated with intraOcular Ranibizumab (PrONTO) study suggest that a flexible dosing regimen with the OCT-measured central retinal thickness (CRT) and VA being used as guiding criteria for re-treatment may be as effective as monthly treatment (Fung et al., 2007). OCT-measured CRT may fulfill the need of a surrogate marker for assessing a fairly accurate re-treatment time when following the “pro re nata” (PRN) treatment schedule.

The SUSTAIN study was designed to further investigate the safety and efficacy of CRT/VA-guided flexible dosing regimen for ranibizumab in AMD patients (Holz et al., 2011).

SUSTAIN showed that a flexible treatment approach with monthly monitoring of lesion activity, based on visual acuity and retinal thickness measures, can on average sustain vision gained after the initial loading phase of three consecutive monthly injections. The overall 12-month safety and tolerability profile of ranibizumab was consistent with that found in other phase III clinical trials with monthly and quarterly dosing of ranibizumab.

More recently, large randomized double-masked studies such as CATT, HARBOR and IVAN (Martin et al., 2012; Busbee et al., 2013; Chakravarthy, et al 2013) with PRN treatment and monthly monitoring demonstrated comparable visual outcomes to monthly injections.

Ranibizumab (intravitreal injections of 0.5 mg) was approved for the treatment of wet age-related macular degeneration (AMD) in June 2006 by the FDA and in January 2007 by the EMA. It is currently approved in more than 110 countries worldwide.

**Visual impairment due to diabetic macular edema (DME)**

Ranibizumab in DME has been studied in several clinical trials.

RESOLVE was the first randomized, double-masked, sham-controlled phase II study of ranibizumab in patients with visual impairment due to DME (Massin et al., 2010). RESOLVE demonstrated that ranibizumab is well tolerated and significantly more effective than sham treatment in rapidly and continuously improving best corrected visual acuity (BCVA) over a period of 12 months. There were no imbalances in the rates of ocular and non-ocular SAEs or AEs between the ranibizumab and sham arms.

READ-2, an investigator-initiated, open-label, laser-controlled, phase II study in patients with visual impairment due to DME, showed that ranibizumab 0.5 mg is superior to laser photocoagulation with respect to BCVA improvement from baseline to Month 6 (Nguyen et al., 2009). After the primary endpoint at month 6, patients were followed up for 18 more months and if retreatment criteria were met, all patients could be treated with 0.5 mg ranibizumab (Nguyen, 2010). Intraocular injections of ranibizumab provided benefit for patients with DME for at least 2 years, and when combined with focal or grid laser treatments, the amount of residual edema was reduced, as were the frequency of injections needed to control edema.
The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a comparative effectiveness randomized clinical trial in 691 study participants (854 study eyes) to evaluate 3 different treatments, including intravitreal 0.5 mg ranibizumab combined with prompt or deferred (≥ 24 weeks) focal/grid laser or 4 mg triamcinolone combined with prompt focal/grid laser, compared with sham injections with prompt focal/grid laser alone for treatment of center-involved diabetic macular edema (DME). The study found that intravitreal ranibizumab with prompt or deferred laser was more effective through at least 1 year compared with prompt laser alone for the treatment of DME involving the central macula, although uncommonly associated with endophthalmitis.

The expanded 2-year results reported are similar to results published previously and reinforce the conclusions originally reported: ranibizumab with prompt or deferred focal/grid laser should be considered for patients with DME with characteristics similar to the cohort in this clinical trial, including vision impairment with DME involving the center of the macula (Elman MJ, Bressler NM, et al., 2011).

The 3-year results from this DRCR.net randomized clinical trial suggest that adding focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better, and possibly worse, for vision outcomes than deferring addition of laser treatment for at least 24 weeks in eyes with DME involving the fovea with vision impairment. These DRCR.net results extend the results from 2 years regarding the continued decreased frequency of intravitreal injections applied while maintaining the visual acuity outcomes noted at 1 and 2 years after initiation of ranibizumab treatment (Elman, et al 2012).

In the phase III RESTORE study, ranibizumab alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12. Ranibizumab was well tolerated as monotherapy or as adjunctive to laser therapy in patients with visual impairment due to DME. The safety profile of ranibizumab in theRESTORE study was similar to that established for neovascular AMD (Mitchell et al., 2011).

The 1-year interim analysis of the RESTORE extension study supports the long-term safety and efficacy of ranibizumab in DME. The safety profile of ranibizumab reported from this interim analysis is consistent with the reported safety profile of ranibizumab in DME. This study confirms that PRN ranibizumab treatment sustains the initial VA gains with declining numbers of injections in the second year (Lang, et al 2013).

Ranibizumab (0.5 mg) was approved in January 2011 by the EMA and in August 2012 by the FDA for the treatment of visual impairment due to diabetic macular edema (DME).
Visual impairment due to macular edema secondary to retinal vein occlusion (RVO)

In the pivotal BRAVO (for BRVO) and CRUISE (for CRVO) studies (Campochiaro et al., 2010; Brown et al., 2010; Campochiaro et al., 2011; Brown et al., 2011), monthly treatment with both 0.3 mg and 0.5 mg ranibizumab applied 6 times at monthly intervals induced rapid BCVA improvement within the first week followed by continued gradual improvement up to Month 6. These studies showed that approximately 60% of BRVO and 48% of CRVO patients treated with monthly ranibizumab gained at least 15 letters of BCVA at 6 months, compared with 29% and 17% of those treated according to current standard practice, respectively. The BCVA gain was maintained on average until Month 12 by the PRN treatment, which was based on BCVA and morphologic parameters. Comparing the effect of 0.3 mg and 0.5 mg ranibizumab, there was a trend toward greater benefit for the 0.5 mg group than for the 0.3 mg group in the mean change from baseline in BCVA score at Month 6. In the CRUISE study (n = 392), 130 patients were treated with 0.5 mg ranibizumab for up to 12 months.

The BRAVO and CRUISE studies demonstrated statistically significant superior VA gain at Month 6 with both doses of ranibizumab as compared to sham control. The observed safety profile of both doses of ranibizumab was consistent with the previously established safety profile of ranibizumab in wet AMD patients and no new ranibizumab or intravitreal injection procedure-related adverse events (AEs) or risks were identified in RVO patients. Patients who completed BRAVO and CRUISE were eligible for entry into a 2-year follow-up study entitled HORIZON. In the HORIZON study, data are collected on a quarterly basis.

Ranibizumab (0.5 mg) was approved in June 2010 by the United States Food and Drug Administration for the treatment of ME following BRVO and CRVO.

Ranibizumab (0.5 mg) was also approved in the European Union for the treatment of ME secondary to RVO in May 2011, based on the above mentioned data from BRAVO and CRUISE.

Visual impairment due to CNV secondary to pathologic myopia (mCNV)

In the phase II, prospective, multicenter REPAIR study in patients with mCNV, the mean change in BCVA score on the ETDRS eye chart was 13.8 letters at 12 months from a baseline level of 59.5 letters (Tufail, et al 2013).

The clinical safety and efficacy of Lucentis in patients with visual impairment due to mCNV have been assessed based on the 12-month data of the randomised, double-masked, controlled pivotal study F2301 (RADIANCE). This study was designed to evaluate 0.5 mg ranibizumab based on a dosing regimen driven by BCVA stabilization criteria and 0.5 mg ranibizumab based on a dosing regimen driven by disease activity in comparison to verteporfin PDT (vPDT, Visudyne photodynamic therapy).

50.9% of patients with a dosing regimen driven by disease activity (which is the recommended posology) required 1 or 2 injections, 34.5% required 3 to 5 injections and 14.7% required 6 to 12 injections over the 12-month study period. 62.9% of the patients did not require injections in the second 6 months of the study.
Both ranibizumab treatment arms demonstrated superior efficacy (10.5 and 10.6 letters VA gain) compared with vPDT (2.2 letters) with respect to mean average change in BCVA from Baseline to Month 1 through Month 3.

Ranibizumab (0.5 mg) was approved in the European Union for the treatment of mCNV in July 2013, based on the above mentioned data from RADIANCE.

1.2 Study Rationale

This 5-year observational study, aiming to recruit 30,000 patients throughout the world is conducted to describe long term safety and effectiveness of ranibizumab in patients treated according to local routine clinical practice in all approved indications worldwide according to the local product label. The study will also describe treatment patterns for ranibizumab and assess the health-related quality of life (HRQoL) of patients treated with ranibizumab in the real world setting for all approved indications according to the local product label.

The results of the study will be used for communication/publication purposes and will also help answering specific questions raised by the Health Authorities in regards to the long term safety of ranibizumab in patients diagnosed with DME, RVO or mCNV and treated with ranibizumab.

2 Study objectives

2.1 Primary objectives

- To describe the safety for all approved indications included in the local product label as observed in this 5-year study duration and assessed by the type, frequency, severity and relationship of all systemic and ocular adverse events
- To describe the effectiveness of ranibizumab in routine clinical practice for all approved indications included in the local product label as observed in this 5-year study duration and assessed by mean change in visual acuity over time and mean change in CRT over time if data allow

2.2 Secondary objectives

- To describe treatment patterns for ranibizumab in routine clinical practice for all approved indications included in the local product label as assessed by overall number of injections, number of visits, time interval between injections, duration of treatment period, number of re-treatment, reasons for re-treatment and reasons for treatment termination
- To assess the HRQoL of patients treated with ranibizumab in routine clinical practice for all approved indications included in the local product label as assessed by the change from baseline in NEI VFQ-25 composite and subscale scores
3 Investigational plan

3.1 Study design

This study is designed as an observational, non-interventional, multicenter, open label, single arm study in patients being treated with ranibizumab for any approved indication included in the local product label. No minimum number of patients per approved indications is intended to be recruited. However, measures may be taken to ensure that the study population appropriately reflects the different indications and the variety of countries where ranibizumab is approved.

Patients treated according to local routine clinical practice will be enrolled in the study upon signing an informed consent.

The baseline visit will be used to assess eligibility and collect baseline characteristics information (refer to Section 6).

The observation period will not be dictated by the protocol. The follow-up visits will take place at a frequency defined as per investigator’s discretion.

All visits should be documented in the CRF. It is recommended that CRFs are completed after every visit and at a minimum of every 3 months post visit.

The overall duration of the study is anticipated to be 5 years, with a minimum of 1 year follow-up period per patient.

A minimum of one visit per year is required in order to maintain a patient’s participation in the study.

3.2 Rationale of study design

An observational study design, without a strict, mandated visit schedule or mandated treatment regimen was chosen as the most appropriate to collect available data in a real life setting in patients previously treated with, treated with, or initiating treatment with ranibizumab for all approved indications in the local product label.

3.3 Rationale of dose/regimen, duration of treatment

The only requirement for participation is that treatment with ranibizumab is for an approved indication included in the local product label.

As this is an observational study to assess safety and effectiveness in routine clinical practice, the only recommendation regarding dose, frequency, or duration of treatment is that patients should be treated with ranibizumab according to the approved local product label.

3.4 Rationale for choice of comparator

No comparator drug will be included in this study.
3.5 Purpose and timing of interim analyses

A first interim look presenting the baseline characteristics of approximately 2000 patients enrolled will be conducted upon enrolment of these patients. This interim look will enable communication on the study and on the patient population enrolled in LUMINOUS™.

During the study 5-year duration, it is planned to evaluate on a regular basis the accumulated data at the time points defined below.

The first interim analysis will take place when all patients enrolled during the first year of recruitment have completed one year of follow-up. Subsequent interim analyses will occur annually thereafter up to the fourth year of the study. Therefore, three interim analyses are planned.

The interim analyses will be performed on all patients with data collected for a minimum of one year follow-up.

These analyses will enable the evaluation of the safety and effectiveness study data on an ongoing basis throughout the study duration.

Interim analyses on other time points may occur as needed.

The results of these interim analyses are not expected to change the study conduct or the patient population.

3.6 Risks and benefits

This study is designed as an observational study where enrolled patients are treated with ranibizumab according to the approved indication(s) included in the local product label. Therefore, the benefit/risk associated with participation in this study is expected to be similar to the one described in the local product label.

4 Population

This study will include consenting adult patients who have previously been treated with, who are currently being treated with, or are initiating treatment with ranibizumab for any approved indication included in the local product label. Patients will include those prospectively enrolled from outpatient ophthalmology clinics in selected countries where ranibizumab is marketed.

It is aimed to recruit a maximum of 30,000 patients in approximately 600 centers worldwide in around 40 countries.

4.1 Inclusion criteria

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

- Adult patients, within age limit as defined by local regulations and local product label, who have previously been treated with, who are currently being treated with, or initiating treatment with ranibizumab for any approved indication included in the ranibizumab local product label; and
• Willing and able to provide informed written consent personally or by legal proxy

4.2 Exclusion criteria
Patients fulfilling any of the following criteria are not eligible for inclusion in the study:
  • Simultaneous participation in a study that includes administration of any investigational drug or procedure
  • Systemic treatment with any VEGF inhibitor in the 90 days prior to study enrollment
  • Ocular treatment with any VEGF inhibitor other than ranibizumab in the month prior to study enrollment

5 Treatment

5.1 Investigational and control treatment
There is no therapy being prescribed or dispensed as part of this study. This observational study does not direct therapy or recommend any treatment other than that patients should be treated in accordance with the approved ranibizumab local product label. Lucentis is a 10 mg/ml ranibizumab solution for injection in a single-use vial. In some countries, Lucentis is also available as a 10 mg/ml solution for injection in a pre-filled syringe for single use.

5.2 Treatment arms
Since this is an observational study, all patients enrolled will receive ranibizumab as per the local approved product label.

5.3 Treatment assignment
Not applicable

5.4 Treatment blinding
Not applicable

5.5 Treating the patient

5.5.1 Patient numbering
Each patient is uniquely identified in the study by a combination of his/her center number and the patient number. The center number is assigned by Novartis or designee to the investigative site.

For sites using eCRF, upon entering the baseline visit data, the patient is assigned a patient number by the eCRF.

For paper CRF, the site is requested to number patients in chronological order following their time of enrolment in the study.
At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). Once assigned to a patient, a patient number will not be reused.

5.5.2 Dispensing the study treatment
Not applicable

5.5.3 Supply, storage and tracking of study treatment
Not applicable

5.5.4 Instructions for prescribing and taking ranibizumab
It is recommended that ranibizumab treatment be administered according to the local approved product label.

All injections of ranibizumab 0.5 mg dispensed to the patient during the study must be recorded on the Dosage Administration Record CRF. The use of the ranibizumab pre-filled syringe, where applicable, should be captured in the relevant CRF section.

If a patient is bilaterally impaired with a condition for which ranibizumab treatment is indicated, the occurrence of bilateral treatment for that same indication will be documented and clinical data will be collected for each eye as per routine clinical practice.

5.5.5 Permitted interruptions of study treatment
It is recommended that any ranibizumab treatment interruptions follow the local approved product label for that particular indication.

5.5.6 Rescue Medication
Not applicable

5.5.7 Concomitant treatment
The investigator should instruct the patient to notify the study site about any new medications he/she takes during the study.

All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient is included in the study must be listed on the Concomitant medications/Significant non-drug therapies CRF.

5.5.8 Prohibited treatment
As this is an observational study, no treatment can be prohibited.

The only requirement is for the ranibizumab local approved product label to be followed.

5.5.9 Premature patient withdrawal from the study
Patients will be withdrawn from the study under the following circumstances:
• Withdrawal of study informed consent
• Pregnancy
• Patient switches to a treatment other than an intravitreal VEGF inhibitor and is no longer receiving ranibizumab treatment in either eye (i.e., as long as the patient is still being treated with ranibizumab in at least one eye, treatment other than an intravitreal VEGF inhibitor is acceptable)
• Patient receives an intravitreal injection with a VEGF inhibitor other than ranibizumab in either eye, regardless of whether ranibizumab is continued in either eye.
• Patient is not seen at the clinic at least once a year

If premature withdrawal occurs for the reasons described above, the investigator should make every effort to record the primary reason for a patient’s premature withdrawal from the study 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.

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

5.5.10 Emergency unblinding of treatment assignment

Not applicable

5.5.11 Study completion

The planned duration of the study is 5 years and patients will be followed until the end of the study unless they discontinue or withdraw from the study.

It is foreseen that study enrollment will stop upon reaching 30,000 patients or at the end of the fourth year whichever comes first. This is to ensure that all patients are followed up for at least one year.

A patient will be considered to have completed the study if they are still observed at the time of study closure.

5.5.12 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 as described in Section 6 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 IRBs and/or IECs of the early termination of the study.
6 Visit schedule, assessments and data collection

Table 6-1 lists all the data to be collected in each patient’s CRF and indicates with an “x” the data when they are collected.

There is no preset visit schedule, i.e. timing of actual patient visits is at the discretion of the treating physicians and sites will have the option of entering data from every patient visit.

Physicians will be encouraged to follow-up with patients who have not been seen in the clinic for at least 6 months since the last visit to capture data as specified in Table 6-1 and again 6 months later if no subsequent visit occurs within the following 6 months.

If patients are not seen at least once per year, they will be discontinued from the study.

All visits should be documented in the CRF. It is recommended that CRFs are completed after every visit and at a minimum of every 3 months post visit. However, any SAEs that are detected at visits occurring between quarterly data collection points, or observed by or reported to the investigator at any time outside of a regularly scheduled visit, will be reported by the investigator according to Section 7.2.

### Table 6-1 Recommended Data Collection Schedule

<table>
<thead>
<tr>
<th>Timing of data collection</th>
<th>Baseline</th>
<th>Observation period</th>
<th>End of study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Recommended at Every Visit; Required at 3 months +/- 1 month</td>
<td>Annually +/- 2 months</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ocular medical history/comorbidities</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular disease history / Relevant medical history / current medical conditions</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior and concomitant medications / significant non-drug therapies</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Prior ocular treatments / therapies</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular examination (e.g. pre-injection IOP)*</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visual acuity in ETDRS or Snellen (preferably best corrected visual acuity)*</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Central retinal thickness*</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ranibizumab treatment given</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SAEs§/AEs</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NEI VFQ-25*</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

* optional (if available). It is recommended that VA is captured for both eyes at baseline and at each time the NEI VFQ-25 questionnaire is administered.
6.1 Information to be collected on screening failures

Not applicable

6.2 Patient demographics and other baseline characteristics

The following data elements will only be collected at baseline:

- Demographic data (e.g., date of birth, gender, race/ethnicity, where permitted under local regulations)
- Non-ocular medical history/comorbidities (based on historical data, current treatment, or clinical judgment), including
  - Cardiovascular/Cerebrovascular events, including
    - Myocardial infarction
    - Stroke
    - Thromboembolic event
    - Obesity
    - Family history of coronary artery disease
    - Hypercholesterolemia/hyperlipidemia
    - Hypertension
    - Diabetes
  - Relevant medical history and current medical conditions including ocular history
    - Date of diagnosis leading to inclusion in the study
    - Date of surgery
    - Site

If a diagnosis and a surgery are both recorded on the CRF for the same condition, both dates should be provided.

- Smoking history
- Prior and concomitant medications / significant non-drug therapies
- Primary indication for initiation of ranibizumab treatment including
  - Eye(s) treated
  - Date(s) of diagnosis of condition in each eye
- Prior ocular treatments / therapies (prior ranibizumab treatment information, prior intravitreal treatments and prior laser therapy) including
  - Type of treatment
  - Eye(s) treated
  - Start and end date of overall treatment period
  - Total number of treatments administered during the reporting period

§ To be collected at visits occurring outside the quarterly +/- 1 month data collection interval
* Refer to Section 6.2 for more specific detailed information
If a patient is bilaterally impaired with a condition for which ranibizumab treatment is indicated, the occurrence of bilateral treatment for that same indication will be documented and clinical data will be collected for each eye.

The following data collection elements are considered *optional* and may be collected if available:

- Ocular examination, if performed as part of routine care
  - Baseline lesion characteristics for wet AMD patients only, including
    - Date of assessment
    - Lesion type and size
    - Anatomical findings

### 6.3 Treatment exposure

Information regarding ranibizumab administration and reason for dosing during the study will be collected on the Dosage Administration Record of the CRF.

Drugs administered prior start of the study and other drugs continuing or started during the study period will be entered on the Prior and concomitant medications / significant non-drug therapies CRF page. Start date, end date, site and reason for administration are to be recorded.

### 6.4 Effectiveness

Effectiveness will be assessed using visual acuity as the functional parameter for all patients and central retinal thickness as the anatomical parameter on available data.

#### 6.4.1 Visual acuity (VA)

Effectiveness of ranibizumab treatment will be described by change in visual acuity from baseline assessed at visits performed per investigator’s discretion. Effectiveness cannot be described if VA at baseline is missing. Therefore it is recommended to document it in the CRF.

VA (preferably best-corrected VA) will be measured according to the method used by the treating physician in the course of local routine care.

VA will be captured in the CRF, according to Table 6-1, allowing use of ETDRS-like or Snellen charts. If a Snellen fraction or decimal score is entered, it will be converted into an approximate ETDRS equivalent letter score for the purpose of statistical analysis (see Section 9.4.1.2). Therefore, it is recommended that ETDRS-like sight charts are used if available.

For consistency and analyses, it is recommended that the same method of VA assessment be used throughout the study wherever possible.

#### 6.4.2 Optical coherence tomography (OCT)

In addition to VA, effectiveness of ranibizumab treatment will also be measured by change in CRT, where available.

CRT collection is optional and will be documented in the CRF as indicated in Table 6-1.
For consistency and analyses’ purposes, it is recommended that the same method of assessment and the same type of OCT machine be used throughout the study wherever possible.

6.4.3 Appropriateness of effectiveness assessments

Visual acuity is selected as it represents the true treatment clinical benefit for the patient populations studied and because it is also a routine clinical practice assessment.

6.5 Safety

Safety evaluations will comprise of the monitoring and assessment of all systemic and ocular adverse events including ophthalmic examinations if performed.

These data will be collected according to the schedule detailed in Table 6-1.

6.5.1 Ophthalmic examinations

Tonometry will be conducted following local routine standard of care practice to assess intraocular pressure (IOP).

If available, only the pre-injection IOP measurement will be recorded in the CRF as indicated in Table 6-1.

6.5.2 Appropriateness of safety assessments

The safety assessments selected are standard for the patient populations studied.

6.6 Other assessments

The following data elements will be collected during the observation period as part of clinical follow-up:

- Ranibizumab treatment status
  - Treatment administration (left/right eye, reason for treatment and date of dosing)
  - Treatment termination, and reason for treatment termination, date of last ranibizumab injection

6.6.1 Health-related Quality of Life (HRQoL)

Administration and collection of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) is considered optional.

The NEI VFQ-25 will be administered with data collected as indicated in Table 6-1. This will be performed where local language versions are available and where they are approved by the corresponding IEC/IRB following local laws and regulations.

The patient’s answers to the interview questions will be recorded in the source document and subsequently transcribed to the CRF.
The NEI VFQ-25 was designed to measure areas of functioning and health status determined to be most important to persons with chronic eye diseases. It is the most widely used PRO instrument to measure HRQoL in studies of patients with eye disease. The NEI VFQ-25 (Appendix 1) can be either interviewer-administered or self-administered, and takes an estimated 10 minutes to complete when interviewer administered (Mangione et al., 2001; Finger et al., 2008).

If consent was provided by the patient, the investigator can administer the questionnaire to his/her patient. It is recommended to begin administration of the questionnaire at baseline and administration should occur prior to any ranibizumab injection to eliminate any confounding factors. The patient’s answers to the interview questions will be recorded in the source document and subsequently transcribed to the CRF.

It is recommended to capture VA of both eyes at baseline and each time the NEI VFQ-25 questionnaire is administered to facilitate the interpretation of the NEI VFQ-25 data.

The majority of the questionnaires used for countries participating in this study are in the interviewer-administered format. Only questionnaires provided in the investigator site file should be administered to the patients.

Any interviewer-administered questionnaire should be administered by the investigator to the patient.

The investigator will assess the interview question responses given by the patient for potential AEs or SAEs (including unsolicited comments from the patient). If the occurrence of AEs or SAEs is confirmed, the investigator must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol. Investigators are encouraged not to prompt the responses to the patients during the interview.

The NEI VFQ-25 is a shortened version of the NEI VFQ-51, and consists of 25 vision-related questions representing 11 vision-related constructs, including global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, driving difficulties, limitations with peripheral vision, limitations with color vision, and ocular pain. In addition, there is a single additional general health rating question shown to be a robust predictor of future health and mortality in population-based studies. In addition to its use in measuring the treatment effect on vision-related function in AMD patients, the NEI VFQ-25 has been used to measure treatment benefits in patients with several ocular conditions, including DME and RVO (Klein et al, 2001).

7 Safety monitoring

The safety recording period starts after providing informed consent except for the non-serious AEs in ranibizumab treatment naïve patients, which are collected from the first injection of ranibizumab.

All adverse events (AEs), including serious adverse events (SAEs), occurring during the safety recording period will be collected and reported in the clinical database irrespective of suspected causal association and according to the processes described below.
In addition, investigators should report adverse reactions suspected to be related to non-Novartis products to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting, or to the Marketing Authorization Holder for that product.

7.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring during the safety recording period even if the event is not considered to be related to ranibizumab.

Medical conditions/diseases present before the safety recording period are only considered adverse events if they worsen during the safety recording period. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

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. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. the site (non-ocular, left eye, right eye, both eyes)
3. its relationship to ocular injection or ranibizumab (suspected/not suspected)
4. its duration (start and end dates or if continuing at final exam)
5. whether it constitutes an SAE

In addition, all reports of the following special scenarios with ranibizumab are also considered an AE irrespective of whether a clinical event has occurred:

- Drug-drug or drug-food interaction
- Drug exposure during pregnancy (see also section 7.3. Pregnancies)
- Drug use during lactation or breast-feeding,
- Lack of effectiveness (as judged by the investigator considering the product information)
- Overdose (the administration of a single dose greater than that specified in the product information, i.e. > 0.5 mg, or, more frequent administration than in the product information, i.e. < 28 days between doses; clinical judgement should always be applied.)
- Drug abuse and misuse
- Drug maladministration or accidental exposure
- Dispensing errors / Medication errors
- Off-label use
- Withdrawal or rebound symptoms
Information on all AEs is included in the individual patient CRF / clinical database. All non-serious AEs, irrespective of causality, are batched and transferred to Novartis Drug Safety and Epidemiology (DS&E) Department on a periodic basis for inclusion in the Novartis safety database. The transfer should occur not less frequently than once a month.

An SAE is defined as an event which:

- 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 the start of study drug
  - 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
- involves the transmission of an infectious agent via a medicinal product

For ranibizumab, AEs which are listed as identified or potential risks in the RMP and have a targeted follow-up are considered of special interest. AEs of special interest (AESI) should be reported within SAE timelines. As per the RMP, only serious ocular events have a targeted follow-up. Since these AESI are all serious events they are already reported in the same manner as SAEs.

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

It is recommended that all adverse events be treated appropriately.

Any action taken to treat an adverse event, including no action taken (i.e. further observation only); ranibizumab dosage adjusted/temporarily interrupted; ranibizumab permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient’s hospitalization prolonged must 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 routine visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to ranibizumab, the interventions required to treat it, and the outcome.
Physicians will be encouraged to follow-up with patients who have not been seen in the clinic for at least 6 months since the last visit to capture any AEs/SAEs that may have occurred since the previous visit, and again 6 months later if no subsequent visit occurs within the following 6 months.

Information about common side effects and adverse reactions observed with ranibizumab can be found in the approved local product label.

7.2 Serious adverse event reporting

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

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

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 Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to ranibizumab, complete the SAE Report Form in English, and send the completed, signed form by fax or by email as a signed pdf document within 24 hours to the local Novartis DS&E Department. The telephone, fax numbers and email addresses of the contact persons in the local department of DS&E, 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 or email receipt confirmation must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the local product label or package insert (new occurrence) and is thought to be related to ranibizumab, a DS&E Department associate may urgently require further information from the investigator for Health Authority reporting.

7.3 Pregnancies

A female patient must be instructed to stop taking ranibizumab if she becomes pregnant during the study and any instructions or recommendations provided in the local approved label should be followed.
The investigator should counsel the patient, discussing the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy as per normal safety reporting of drug exposure during pregnancy.

To ensure patient safety, **all pregnancy cases** regardless of their seriousness criteria or outcome in patients treated with ranibizumab **must be reported to Novartis within 24 hours of learning of their 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 or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to ranibizumab of any pregnancy outcome.

Any SAE experienced during pregnancy must be reported on the Serious Adverse Event Report Form; see **Section 7.2.**

### 7.4 Data Monitoring Committee

No data monitoring committee will be used for this study.

### 8 Data review and database management

All activities described in this section will be performed by the CRO, Outcome Sciences, on behalf of Novartis.

#### 8.1 Site monitoring

Before study initiation, at a site initiation visit, the CRO representative (Outcome Sciences) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor may visit the site to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Pharmacoepidemiology Practices (GPP), documentation of SAEs and the progress of enrollment. 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. 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. 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

Depending on site’s technical capabilities, sites will have the possibility to enter study information in electronic Case Report Forms (eCRF) or paper Case Report Forms (pCRF).

For sites using pCRF:

Designated investigator staff must enter the information required by the protocol onto the study pCRFs that are printed on 3-part, non-carbon-required paper if applicable. Field monitors will review the pCRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The pCRFs are forwarded to the CRO working on behalf of Novartis (Outcome Sciences) by the investigational site, with one copy being retained at the investigational site. Once the pCRFs are received by the CRO working on behalf of Novartis (Outcome Sciences), 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.

For sites using eCRF:

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 if applicable. Designated investigator site staff will not be given access to the eCRF 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 (Outcome Sciences). The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive a CD-ROM or a DVD or paper copies of the patient data for archiving at the investigational site.

8.3 Data management and quality control

For pCRFs

Where applicable, data from the pCRFs are entered into the study database by CRO staff (Outcome Sciences) 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. 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 pCRFs 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.
For eCRF

As required, the CRO working on behalf of Novartis (Outcome Sciences) reviews the data entered into the eCRFs 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. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to the CRO working on behalf of Novartis (Outcome Sciences) who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Planned database locks (DBL) other than final DBL

For the planned interim analyses, interim DBL will be performed and the clinical database will be frozen to enable the execution of the statistical analyses for the interim analyses as described in the study data management plan. The clinical database will be then re-opened to allow further data entry. However, all requested data changes post-data release will be documented on the database errata log and approved as described in the study data management plan.

9 Data Analysis

The statistical section below describes analyses as planned at interim database snapshots and the final database lock.

The analyses will be performed by the designated CRO or by Novartis Biostatistics and Statistical Reporting department.

The following subgroups will be considered for the analyses: indication, pre-treatment status and time period (duration of 1 to 4 years). The time period considered for a patient will be the floor number of years since this patient entered in the study at the time of the analysis considered.

The analyses will be presented overall. The analyses will only be presented by country and/or region if sample size is sufficient.

Additional exploratory descriptive and inferential analyses of the data will be conducted as deemed appropriate.

Descriptive analyses will include n, mean, standard deviation, median, first quartile, third quartile and ranges for continuous variables and frequencies and percentages for categorical variables. Summaries will be presented together with estimates and corresponding 95% confidence intervals (CI) as appropriate. Complete analytical specifications will be fully detailed in the statistical analysis plan (SAP).
9.1 Analysis sets

The enrolled set will include all patients having signed the informed consent, and with at least a baseline assessment.

All statistical analyses will be carried out on the safety analysis set, including those patients who provide consent to collect information and who were treated with at least one dose of ranibizumab during this study or prior to start of study and had at least one safety assessment after the first treatment. Of note, the statement that a patient had no AE also constitutes a safety assessment.

The primary treated eye set will include all primary treated eyes.

The secondary treated eye set will include all secondary treated eyes.

The fellow eye set will include all fellow eyes.

The primary treated eye will be the first treated eye with ranibizumab during the study (patients may be treated in both eyes).

If the other eye was pre-treated or is treated during the study with ranibizumab then it will be considered as the secondary treated eye; otherwise, this eye will be designated as fellow eye. Therefore, the fellow eye always refers to a non-ranibizumab-treated eye including information prior to study entry visit / treatment history. The relevance of analysis on the secondary treated eye set will be assessed during the interim analyses, based on the amount of data available and its adding value related to safety. Otherwise, only for the final analysis, analyses based on eyes will be presented:

- for safety: on the primary treated eye set, secondary treated eye set and fellow eye set
- for efficacy: on the primary treated eye set and the secondary treated eye set.

9.2 Patient demographics and other baseline characteristics

All patient demographics, medical history, ocular disease history and characteristics, prior treatments, and other baseline characteristics will be presented using standard descriptive statistics.

9.3 Treatments (ranibizumab, concomitant therapies)

The number of ranibizumab injections administrated overall, over time and the average time interval (in weeks) between consecutive injections will be summarized for the primary treated eye set and the secondary treated eye set.

The reasons for treatment /termination will also be summarized.

Visit frequency and treatment patterns will be characterized.

9.3.1 Bilateral treatment

The number of patients who received bilateral injections of ranibizumab (primary treated eye and secondary treated eye) within 14 days and 28 days will be summarized.
9.3.2 Concomitant therapies

The number and percentage of patients taking non-ocular concomitant medications and non-ocular non-drug therapies will be summarized by Preferred Terms (PT). Ocular concomitant medications and ocular non-drug therapies will be considered by eyes.

9.4 Analysis of the primary variable(s)

9.4.1 Variables

9.4.1.1 Safety variables

The primary safety objective of this study will be assessed based on the incidence rate, relationship and severity of treatment emergent ocular and non-ocular adverse events during defined time periods (duration of 1 year to 4 years).

Non-ocular adverse events will be assessed for the safety set; ocular adverse events will be assessed for the primary treated eye set.

A treatment emergent adverse event is defined as any adverse events that started on or after the first ranibizumab treatment of the primary treated eye if this eye was ranibizumab treatment naïve, and any adverse event started on or after the baseline visit if the primary treated eye was pre-treated with ranibizumab.

Incidence rate is calculated as the number of patients (or eyes) with at least one occurrence of a specific event during the safety observation period, divided by the total number of patients (or eyes) observed in the study period, multiplied by 100.

The safety observation period will be described by patient for the primary treated eye.

For patients/eyes naïve to ranibizumab treatment, the safety observation period starts with the date of the first injection while for patients/eyes treated with ranibizumab prior to enrollment, the safety observation period starts with the baseline study entry visit.

AEs related to identified and potential risks as listed in the RMP will be included in this analysis. For each analysis, the last RMP version available will be used. Point estimates for the incidences of those AEs as well as two sided 95% confidence intervals will be provided (Clopper-Pearson method).

The analysis of the SAEs, AEs, and SAEs/AEs related to identified and potential RMP risks will include the following:

- Incidence rate of SAEs, AEs, and SAEs/AEs related to identified and potential RMP risks by System Organ Class (SOC) and Preferred Term (PT) within SOC
- Incidence rate of SAEs, AEs, and SAEs/AEs related to identified and potential RMP risks by SOC and by PT within SOC, according to relationship to ranibizumab, ocular injection, ranibizumab and/or ocular injection.

9.4.1.2 Efficacy variables

The primary efficacy variable will be the mean change in visual acuity (VA) at quarterly intervals from the baseline visit for the primary treated eye set.
VA will be measured according to the method used by each participating physician in his/her routine practice. To be able to integrate different VA assessment methods for analysis, VA assessments performed using Snellen fraction or decimal score will be converted into an approximate ETDRS letter score equivalent.

Mean change in CRT over time by type of OCT machine (spectral domain or time domain) at quarterly intervals from the baseline visit will be summarized for primary treated eye set and for the secondary treated eye set. As CRT data are optional, this analysis will be performed only if data allow.

The number of ranibizumab treatments by patient and by primary treated eye will be summarized.

9.4.2 Statistical model, hypothesis, and method of analysis

In this observational study no statistical hypothesis testing is intended.

The primary safety analysis will be the estimation of incidences rate of non-ocular adverse events by patient and ocular adverse events by primary treated eyes of all adverse events and adverse events related to identified and potential RMP risks. Adverse events will be summarized by presenting the number and percentage of patients experiencing adverse events by system organ class, preferred term and severity of adverse events. In addition, 95% confidence intervals (Clopper-Pearson exact method) for the incidences rate of adverse events related to identified and potential RMP risks will be calculated. The primary efficacy variable is the mean change in VA at quarterly intervals from the baseline visit. This change will be summarized over time for the primary treated eye set.

Both primary objectives will be interpreted with respect to the related number of treatments.

9.4.3 Handling of missing values/censoring/discontinuations

Analysis of complete data as well as additional analyses to evaluate the impact of missing data on the validity of conclusions will be conducted.

The analysis of adverse events will be based on observed data.

The analysis of mean change in VA over time will be based on observed data and Last Observation Carried Forward (LOCF) method.

Further details on how missing data will be handled will be outlined in the SAP.

9.4.4 Supportive analyses

Not applicable.
9.5 Analysis of secondary variables

9.5.1 Secondary variables

The description of treatment patterns associated with ranibizumab as defined in Section 9.3 and the quality of life for patients treated with ranibizumab as assessed by the change from baseline in the composite and subscales cores of the NEI VFQ-25 (refer to Section 9.5.4) will be considered as secondary variables.

9.5.2 Efficacy variables

In completion to the analysis of the primary efficacy parameters, change in VA for the secondary treated eye set, categorized change in VA will serve as secondary efficacy parameters.

The mean change in VA at quarterly intervals from the baseline visit (study entry visit) will be presented for the secondary treated eye set.

For the secondary treated eye set, the baseline visit will be defined as study entry visit (if there was a diagnosis of AMD/DME/RVO/mCNV for the secondary treated eye at that time point) or the visit with the first injection for the secondary treated eye (if no diagnosis at the study entry visit reported for the secondary treated eye).

- Descriptive statistics will be provided for categorized VA annually for the primary treated eye set. Proportion of patients with a VA score \( \geq 73 \) letters
- Proportion of patients with a gain in VA of \( \geq 1 \) letter
- Proportion of patients with a gain in VA of \( \geq 5 \) letters
- Proportion of patients with a gain in VA of \( \geq 10 \) letters
- Proportion of patients with a gain in VA of \( \geq 15 \) letters
- Proportion of patients with a loss in VA of \( < 15 \) letters
- Proportion of patients with a loss in VA of \( < 30 \) letters

9.5.3 Safety variables

In completion to the analysis of the primary safety parameters, incidence rate of AEs by 100 patient-year, incidence rate of AEs starting after the first occurrence of bilateral treatment within 14 days and 28 days, and IOP data will be summarized.

The safety observation period will be described for the secondary treated eye.

9.5.3.1 Adverse events

Incidence rate per 100 patient years is calculated as the number of events occurring during the safety observation period, divided by the total number of patient-years of the safety observation period, multiplied by 100. The 95% CI of the incidence rate will be constructed assuming the frequency of a particular event in a given period of time follows a Poisson distribution. Incidence rate per patient-year of SAEs, AEs, and SAEs/ AEs related to identified and potential RMP risks AEs by SOC and by PT within SOC will be summarized.
In addition, if deemed relevant, a separate analysis of incidences of adverse events in patients receiving bilateral injections of ranibizumab will be performed.

For those patients who withdraw from the study, the analyses will include all data collected up to 30 days after study discontinuation unless explicitly stated otherwise. SAEs collected after the final database lock will not be included in the analysis but reported in the clinical study report.

9.5.3.2 Tonometry

Absolute values and changes in IOP pre-injection will be presented descriptively over time. As IOP data are optional, this analysis will be performed only if data allow.

9.5.4 Health-related Quality of Life

The NEI VFQ-25 can be collected at baseline and annually thereafter.

The NEI VFQ-25 will be scored according to the scoring manual for the instrument (Mangione et al., 2001). In summary, the NEI VFQ-25 (Appendix 1) yields a total score and 11 visual subscale scores: general vision, ocular pain, near vision, distance vision, social function, mental health, role limitations, dependency, driving, color vision, and peripheral vision. Each item is scored from 0 to 100, with higher scores representing higher functioning. Items within each subscale are then averaged together to create the 11 subscale scores, respectively. The composite score is derived by averaging all the subscale scores (Mangione CM, 2000).

Consistent with the developers’ instructions and previous publications, the total score will be computed without including the general health item.

Descriptive statistics including change from baseline will be provided over time for the composite score and subscales scores. Further exploratory analysis of the NEI VFQ-25 data will be conducted, adjusting for VA in both eyes (better- and worse-seeing eye). The results will be summarized separately from the CSR.

9.6 Sample size description

The following section will describe the precision that can be obtained for the primary safety endpoint and the primary efficacy endpoint for different numbers of patients/eyes (n): 500, 1,000, 2,000, 5,000 or 10,000. These numbers are in reference to the analyses including subgroup analyses driven by indication, pre-treatment status, time-period, country. The precision regarding the 95% confidence interval (CI) for AE incidence rate for each n is presented in Table 9-1.

To investigate the width of exact confidence intervals (Clopper-Pearson) for binomial probabilities based on 500, 1000, 2000, 5000 and 10,000 patients/eyes, the following table displays 95% CI for observed 1% and 5% incidence rate.
Table 9-1 95% exact CI for 1% and 5% incidence rate by number of patients/eyes considered

<table>
<thead>
<tr>
<th>n</th>
<th>Observed incidence rate</th>
<th>Observed number of events</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>1%</td>
<td>5</td>
<td>(0.3%, 2.3%)</td>
</tr>
<tr>
<td>500</td>
<td>5%</td>
<td>25</td>
<td>(3.3%, 7.3%)</td>
</tr>
<tr>
<td>1,000</td>
<td>1%</td>
<td>10</td>
<td>(0.5%, 1.8%)</td>
</tr>
<tr>
<td>1,000</td>
<td>5%</td>
<td>50</td>
<td>(3.7%, 6.5%)</td>
</tr>
<tr>
<td>2,000</td>
<td>1%</td>
<td>20</td>
<td>(0.6%, 1.5%)</td>
</tr>
<tr>
<td>2,000</td>
<td>5%</td>
<td>100</td>
<td>(4.1%, 6.0%)</td>
</tr>
<tr>
<td>5,000</td>
<td>1%</td>
<td>50</td>
<td>(0.7%, 1.3%)</td>
</tr>
<tr>
<td>5,000</td>
<td>5%</td>
<td>250</td>
<td>(4.4%, 5.6%)</td>
</tr>
<tr>
<td>10,000</td>
<td>1%</td>
<td>100</td>
<td>(0.8%, 1.2%)</td>
</tr>
<tr>
<td>10,000</td>
<td>5%</td>
<td>500</td>
<td>(4.6%, 5.4%)</td>
</tr>
</tbody>
</table>

The estimated standard deviation for the change in BCVA from baseline to Month 24 is based on the results from the phase IV study SECURE (CRFB002A2402). A dropout rate of about 11% is considered given the study period.

Assuming a standard deviation of 14 letters for the (normal distributed) change in VA from baseline to Month 24, **Table 9-2** below describes the precision of a 2-sided 95% confidence interval (mean change in VA from baseline to Month 24 plus or minus precision) for a n of 500, 1,000, 2,000, 5,000, 10,000 patients.

Table 9-2 Precision of 2-sided 95% confidence interval by number of patients considered

<table>
<thead>
<tr>
<th>n</th>
<th>Precision of 2-sided 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>1.2 letters</td>
</tr>
<tr>
<td>1,000</td>
<td>0.9 letters</td>
</tr>
<tr>
<td>2,000</td>
<td>0.6 letters</td>
</tr>
<tr>
<td>5,000</td>
<td>0.4 letters</td>
</tr>
<tr>
<td>10,000</td>
<td>0.3 letters</td>
</tr>
</tbody>
</table>

9.7 Power for analysis of key secondary variables

Not applicable

9.8 Interim analyses

The interim look and interim analyses planned in the study will be performed as described in Section 3.5.

Publication of the interim look and interim analysis results is foreseen, but it is not anticipated to lead to changes in the study conduct.

The results of the interim analyses could drive additional ad-hoc analyses.
From the first interim analysis onwards, interim analyses will be a full analysis as described in Section 9 of the protocol including exposure, safety, efficacy and QoL, dependent on the amount of data available. For the efficacy analysis, only the primary treated eye set will be presented.

For these interim analyses, only patients with at least one year of follow-up will be analyzed. For the time period subgroups, patients will be grouped according to the number of full years since they entered the study, at the time of the database snapshot. For each patient only the data from this corresponding year period will be considered for the analysis. For example, for a patient having 14 months of follow-up at the time of the interim analysis, only the first 12 months will be considered for this patient, and will enter in the time period analysis of one year. From one interim analysis to the next, the same subset of patients by time period will be considered, with the time period incremented by one year, even if a patient drops out during this period i.e. the 4-year time period will not be restricted to patients having completed a full 4-year study.

For each interim analysis, the different time periods can be considered simultaneously (e.g. for the third IA, the time periods considered will be 1 year, 2 years and 3 years follow-up).

10 Ethical and regulatory considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the ethical principles laid down in the Declaration of Helsinki, and any applicable national guidelines.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data.

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 (if required by local regulations) 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 data collection (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 or the CRO working on behalf of Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the relevant guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC where applicable, and a copy of the approved version must be provided to the CRO monitor after IRB/IEC approval if relevant.

10.3 Responsibilities of the investigators and IRB/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 (IRB/IEC) before study start, or alternatively IRB/IEC notification will be performed, as appropriate in accordance with local laws and regulations. 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 where applicable.

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/REBs, 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. Results from interim analyses may be published prior to study completion.

Throughout the study, individual investigators will have access to their own patients’ data. Study investigators will be permitted to publish their own patient’s data subsequent to study level publication. Publications will be developed based on guidance provided by the sponsor. Notification to the sponsor and approval by the LUMINOUS™ Steering Committee (LSC) as defined in the LSC publication process flow and site level contracts is required.

11 Protocol adherence

This observational study protocol does not direct therapy or dictate any treatment other than that patients be treated in accordance with the ranibizumab approved local product label. Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the clinical study report.
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 and the IRB/IEC, where required. 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 and the CRO (Outcome Sciences) should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

11.2 Study governance

The LUMINOUS™ Steering Committee (LSC) is formed as a permanent body comprised of retina experts selected from participating countries.

The LSC will serve in an advisory role to Novartis Pharma AG and the LUMINOUS™ study sites.

This group of leading experts in the field of retinal diseases from different countries included in the study will provide scientific guidance on the design of the protocol and any protocol amendments.

These experts will also advise on the conduct, enrollment, and analysis of the study as appropriate.

The LSC will have oversight of the results generated by the study and will advise and support Novartis to achieve high quality publications as defined in the Steering Committee charter.

12 References


Bressler NM (2004) Age-related macular degeneration is the leading cause of blindness. JAMA; 291:1900-1901.


13 Appendix 1: NEI VFQ-25 (self-administered format)
PB/SA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

RAND hereby grants permission to use the ‘National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25)’ July 1996, in accordance with the following conditions which shall be assumed by all to have been agreed to as a consequence of accepting and using this document:

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The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.

2. Please answer every question (unless you are asked to skip questions because they don’t apply to you).

3. Answer the questions by circling the appropriate number.

4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.

5. Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.

6. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.
Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:
   
   (Circle One)
   
   Excellent ........................................ 1
   Very Good ........................................ 2
   Good .............................................. 3
   Fair ............................................... 4
   Poor .............................................. 5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?
   
   (Circle One)
   
   Excellent ........................................ 1
   Good .............................................. 2
   Fair ............................................... 3
   Poor .............................................. 4
   Very Poor ..................................... 5
   Completely Blind ............................. 6
3. How much of the time do you worry about your eyesight?

(Circle One)

None of the time ........................................ 1
A little of the time ..................................... 2
Some of the time ....................................... 3
Most of the time ....................................... 4
All of the time? ......................................... 5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None..................................................... 1
Mild..................................................... 2
Moderate................................................. 3
Severe, or .............................................. 4
Very severe?........................................... 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(Circle One)

No difficulty at all ........................................ 1
A little difficulty ........................................ 2
Moderate difficulty .................................... 3
Extreme difficulty ..................................... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this......................................... 6

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6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)

No difficulty at all .............................................. 1
A little difficulty .................................................. 2
Moderate difficulty ............................................... 3
Extreme difficulty ............................................... 4
Stopped doing this because of your eyesight .... 5
Stopped doing this for other reasons or not interested in doing this.................................6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)

No difficulty at all .............................................. 1
A little difficulty .................................................. 2
Moderate difficulty ............................................... 3
Extreme difficulty ............................................... 4
Stopped doing this because of your eyesight .... 5
Stopped doing this for other reasons or not interested in doing this.................................6

8. How much difficulty do you have reading street signs or the names of stores?

(Circle One)

No difficulty at all .............................................. 1
A little difficulty .................................................. 2
Moderate difficulty ............................................... 3
Extreme difficulty ............................................... 4
Stopped doing this because of your eyesight .... 5
Stopped doing this for other reasons or not interested in doing this.................................6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

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version 2000

(Circle One)

No difficulty at all .................................................. 1
A little difficulty .................................................... 2
Moderate difficulty .................................................. 3
Extreme difficulty .................................................... 4
Stopped doing this because of your eyesight .... 5
Stopped doing this for other reasons or not interested in doing this ........................................... 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

No difficulty at all .................................................. 1
A little difficulty .................................................... 2
Moderate difficulty .................................................. 3
Extreme difficulty .................................................... 4
Stopped doing this because of your eyesight .... 5
Stopped doing this for other reasons or not interested in doing this ........................................... 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

No difficulty at all .................................................. 1
A little difficulty .................................................... 2
Moderate difficulty .................................................. 3
Extreme difficulty .................................................... 4
Stopped doing this because of your eyesight .... 5
Stopped doing this for other reasons or not interested in doing this ........................................... 6

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12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)

No difficulty at all .................................................. 1
A little difficulty .................................................... 2
Moderate difficulty .................................................. 3
Extreme difficulty .................................................... 4
Stopped doing this because of your eyesight .... 5
Stopped doing this for other reasons or not interested in doing this ........................................ 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

(Circle One)

No difficulty at all .................................................. 1
A little difficulty .................................................... 2
Moderate difficulty .................................................. 3
Extreme difficulty .................................................... 4
Stopped doing this because of your eyesight .... 5
Stopped doing this for other reasons or not interested in doing this ........................................ 6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(Circle One)

No difficulty at all .................................................. 1
A little difficulty .................................................... 2
Moderate difficulty .................................................. 3
Extreme difficulty .................................................... 4
Stopped doing this because of your eyesight .... 5
Stopped doing this for other reasons or not interested in doing this ........................................ 6

15. Are you currently driving, at least once in a while?

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15a. IF NO: Have you never driven a car or have you given up driving?

(Circle One)

Yes ...................... 1  Skip To Q 15c
No ...................... 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ....................... 1  Skip To Part 3, Q 17
Mainly other reasons .................... 2  Skip To Part 3, Q 17
Both eyesight and other reasons .... 3  Skip To Part 3, Q 17

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all ......................... 1
A little difficulty ......................... 2
Moderate difficulty ....................... 3
Extreme difficulty ....................... 4
16. How much difficulty do you have driving at night? Would you say you have:

(Circle One)

No difficulty at all........................................ 1
A little difficulty......................................... 2
Moderate difficulty..................................... 3
Extreme difficulty...................................... 4
Have you stopped doing this because of your eyesight................................. 5
Have you stopped doing this for other reasons or are you not interested in doing this........................................ 6

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:

(Circle One)

No difficulty at all........................................ 1
A little difficulty......................................... 2
Moderate difficulty..................................... 3
Extreme difficulty...................................... 4
Have you stopped doing this because of your eyesight................................. 5
Have you stopped doing this for other reasons or are you not interested in doing this........................................ 6
PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

<table>
<thead>
<tr>
<th>READ CATEGORIES</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Do you accomplish less than you would like because of your vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18. Are you limited in how long you can work or do other activities because of your vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
For each of the following statements, please circle the number to indicate whether for you the statement is **definitely true**, **mostly true**, **mostly false**, or **definitely false** for you or you are **not sure**.

*(Circle One On Each Line)*

<table>
<thead>
<tr>
<th>Statement</th>
<th>Definitely True</th>
<th>Mostly True</th>
<th>Not Sure</th>
<th>Mostly False</th>
<th>Definitely False</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. I stay home most of the time because of my eyesight. ....................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>21. I feel <strong>frustrated</strong> a lot of the time because of my eyesight ..........</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>22. I have <strong>much less control</strong> over what I do, because of my eyesight ....</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>23. Because of my eyesight, I have to rely too much on what other people tell me...</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>24. I need a lot of help from others because of my eyesight ..................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>25. I worry about <strong>doing things</strong> that will embarrass myself or others, because of my eyesight ............................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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