

Clinical Development

Ranibizumab/Lucentis<sup>®</sup>

Protocol CRFB002A2412

**A 24-month, phase IV, randomized, double masked,  
multi-center study of ranibizumab monotherapy or  
ranibizumab in combination with verteporfin  
photodynamic therapy on visual outcome in patients with  
symptomatic macular polypoidal choroidal vasculopathy**

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## List of abbreviations

AE	Adverse Event
AMD	Age-related Macular Degeneration
BCVA	Best-corrected Visual Acuity
BVN	Branch Vascular Network
CNV	Choroidal Neovascularisation
CSFT	Central subfield thickness
eCRF	electronic Case Report/Record Form
CPO	Country Pharma Organization
CRO	Contract Research Organization
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
FA	Fluorescein Angiography
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICGA	Indocyanine Green Angiography
IEC	Independent Ethics Committee
IIS	Integrated Information Sciences
i.v.	intravenous
IRB	Institutional Review Board
OCT	Optical Coherence Tomography
PCV	Polypoidal Choroidal Vasculopathy
PDT	Photodynamic Therapy
QoL	Quality of Life
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
VEGF	Vascular Endothelial Growth Factor

## Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls.  This <i>includes</i> any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination.
Label	Product information/Prescribing information
Medication label	Label attached to the outer packaging of the study drug
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug/treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Study eye	The study eye is the eye selected by the investigator at screening to receive study treatment for the purpose of evaluating the study objectives
Total Lesion Area	BVN plus polyps
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

## Amendment 1

### Amendment rationale

Following Health Authority review of the protocol, a non-substantial amendment was issued to clarify some aspects of the protocol and to ensure that the study conduct is fully aligned with locally approved labels. In this context, minor revisions were done to the exclusion criteria and clarifications were provided around the study drug administration and retreatment algorithm. The trial is ongoing, approximately 2% of patients have been enrolled to date. Based on available data, none of the enrolled patients are affected and no impact on the study population as whole or the patients' safety is expected as a result of the protocol revisions.

### Changes to the protocol

#### Changes to Section Exclusion criteria

- Exclusion criterion No. 7: Clarification was added that not only patients with a history of porphyria but also patients with (current) porphyria must be excluded from the trial.
- Exclusion criterion No. 17 (study eye): Wording was added to ensure that not only patients with (confirmed) ocular and periocular infections but also those with **suspected** ocular and periocular infections will be excluded from the trial in consistency with the label wording.

#### Changes to Section 5.5.6 Treatment regimen for the study eye

- The wording was revised for better understanding of the requirement to administer verteporfin and ranibizumab on the same day if applicable.
- Clarification was added regarding the lesion size to be treated with PDT, in alignment with the instructions provided at the Investigator meeting. This change was also implemented in Section 6.4.2
- Footnotes were added to Figure 5-1 (re-treatment algorithm) to provide more detailed instructions on how to make treatment decisions. Footnotes were aligned with those in Tables 6-1 and 6-2

#### Changes to Section 5.5.7 Treatment regimen for the fellow eye

- Clarification was added that while in principal treatment with ranibizumab of both eyes on the same days is allowed, it must be avoided at **initial treatment**.

#### Changes to Section 5.5.11 Prohibited treatment

- Glaucoma filtering surgery was included in "intraocular surgery".
- Table 5-2 was aligned with the text in Section 5.5.11.
- The action to be taken in case of an unavoidable intraocular surgery (e.g. cataract surgery) during the study was changed from "study discontinuation" to temporary withholding of study treatment in order in to ensure patients could still benefit from study treatment.

#### Changes to Section 6.4.5

- Minor revisions to align procedures in the protocol with the Study Operations Manual.

In addition to above changes, other minor (typographical) errors were corrected.



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.

The changes described in this amended protocol may require IRB/IEC approval prior to implementation. In addition, if 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.

## Protocol synopsis

<b>Protocol number</b>	RFB002A2412
<b>Title</b>	A 24-month, phase IV, randomized, double masked, multi-center study of ranibizumab monotherapy or ranibizumab in combination with verteporfin photodynamic therapy on visual outcome in patients with symptomatic macular polypoidal choroidal vasculopathy
<b>Brief title</b>	Study of ranibizumab monotherapy or ranibizumab in combination with verteporfin photodynamic therapy on visual outcome in patients with symptomatic macular polypoidal choroidal vasculopathy
<b>Sponsor and Clinical Phase</b>	Novartis Phase IV
<b>Investigation type</b>	Drug (biologic); drug (photosensitizer)
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	The purpose of this study is to compare the effect of ranibizumab administered as monotherapy vs. ranibizumab administered in combination with verteporfin PDT on visual acuity in patients with symptomatic macular PCV with treatment guided by predefined retreatment criteria. In addition, the study will explore potential correlations between retinal anatomical features and visual acuity. The results of this study will provide long-term safety and efficacy data used to generate further guidance on the management of patients with PCV
<b>Primary Objectives</b>	The primary objective is to demonstrate that ranibizumab combined with verteporfin PDT is non-inferior to ranibizumab monotherapy in patients with symptomatic macular PCV as assessed by the change in best corrected visual acuity (BCVA) from baseline to Month 12 and superior with respect to complete polyp regression assessed by ICGA at Month 12. If this is established, the next step will be to demonstrate that ranibizumab combined with verteporfin PDT is superior to ranibizumab monotherapy as assessed by the change in best corrected visual acuity (BCVA) from baseline to Month 12
<b>Secondary Objectives</b>	All secondary efficacy objectives will be evaluated in the study eye: <ol style="list-style-type: none"> <li>1. To evaluate the change from baseline in BCVA over time up to Month 24.</li> <li>2. To evaluate the proportion of patients with <math>\geq 5</math>, <math>\geq 10</math>, and <math>\geq 15</math> letter increase in BCVA from baseline up to Month 24.</li> <li>3. To evaluate the proportion of patients with a BCVA loss of <math>&lt; 5</math>, <math>&lt; 10</math>, <math>&lt; 15</math>, and <math>&lt; 30</math> letters in BCVA from baseline up to Month 24.</li> <li>4. To evaluate the proportion of patients who have maintained their BCVA (within 5 letter change) at Month 12 and 24 compared to the BCVA at the time point of first ranibizumab treatment interruption.</li> <li>5. To evaluate the change in BCVA at Month 12 and 24 compared to the time point of first ranibizumab treatment interruption.</li> <li>6. To evaluate the proportion of patients with complete polyp regression as assessed by ICGA at Months 6, and 24.</li> </ol>

	<ol style="list-style-type: none"> <li>7. To evaluate the proportion of patients with presence of leakage as assessed by FA at Month 6, 12, and 24.</li> <li>8. To evaluate the changes in central subfield thickness (CSFT) by SD-OCT from baseline over time</li> <li>9. To evaluate the total number of treatments with ranibizumab and verteporfin PDT in the study eye received from baseline up to Month 12 and up to Month 24.</li> <li>10. To evaluate the number of treatments with ranibizumab in the study eye received from Month 3 up to Month 12 and up to Month 24.</li> <li>11. To evaluate Vision-related QOL by means of the VFQ-25 assessed at baseline, Months 3, 12, and 24.</li> <li>12. To evaluate safety and tolerability up to Month 12 and Month 24.</li> </ol>
<b>Study design</b>	This study will use a two-arm, parallel-group, randomized, double-masked design. There will be 4 periods in this study: the Screening Period, Treatment Period 1, Treatment Period 2, and the Post-treatment Follow-up Period. The overall study duration for each patient will be 24 months.
<b>Population</b>	The study population will consist of a group of adults $\geq 18$ years with symptomatic macular PCV who are naïve to treatment of PCV and CNV due to wet AMD in the study eye. The anticipated screening failure rate is approximately 20%; therefore, approximately 400 patients are expected to be enrolled into the study in order to randomize 320 patients.
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Male or Female <math>\geq 18</math> years of age</li> <li>• Confirmed diagnosis of symptomatic macular PCV in the study eye defined by: <ul style="list-style-type: none"> <li>• Active macular polypoidal lesions shown by ICGA AND</li> <li>• Presence of serosanguinous maculopathy (i.e. exudative or hemorrhagic features involving the macula on fundus examination and FA)</li> </ul> </li> <li>• BCVA letter score between 78-24 (approximately 20/32 to 20/320 Snellen equivalent) using ETDRS visual acuity chart measured at 4 meters</li> <li>• Greatest Linear Dimension (GLD) of the total lesion area (BVN + polyps) <math>&lt; 5400 \mu\text{m}</math> (<math>\sim 9</math> MPS Disc Areas) as delineated by ICGA</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Previous treatment with systemic anti-VEGF drugs within 6 months prior to Baseline (e.g., sorafenib [Nexavar<sup>®</sup>], sunitinib [Sutent<sup>®</sup>], bevacizumab [Avastin<sup>®</sup>])</li> </ul> <p>Study eye:</p> <ul style="list-style-type: none"> <li>• Active ocular inflammation or infection (ocular or periocular)</li> <li>• Uncontrolled intraocular hypertension or glaucoma (IOP <math>\geq 30</math> mmHg) despite treatment with anti-glaucoma medication</li> <li>• Ocular disorders in the study eye (e.g. cataract, retinal vascular occlusion, diabetic retinopathy) that, in the opinion of the investigator may confound interpretation of study results or compromise VA or require medical or surgical intervention during the study period</li> <li>• Prior treatment with verteporfin PDT, external-beam radiation, subfoveal or extrafoveal focal laser photocoagulation, submacular surgery, or transpupillary thermotherapy</li> <li>• Prior treatment with any anti-VEGF compound or any investigational</li> </ul>

	<p>treatment</p> <ul style="list-style-type: none"> <li>• Treatment with intravitreal or subtenon corticosteroid injection or device implantation within 90 days prior to screening</li> </ul>
<b>Investigational and reference therapy</b>	<p>On Day 1, patients will be assigned in a 1:1 ratio to one of the following two treatment arms:</p> <ul style="list-style-type: none"> <li>• Ranibizumab monotherapy: Ranibizumab (0.5 mg) plus sham PDT</li> <li>• Ranibizumab combination therapy: Ranibizumab (0.5 mg) plus verteporfin PDT</li> </ul> <p>Ranibizumab is administered by intravitreal injection at a dose of 0.5mg</p> <p>Verteporfin PDT is administered as intravenous infusion (6 mg/m<sup>2</sup>) followed by laser light at a dose rate of 600 mW/cm<sup>2</sup> delivered for 83 seconds (light dose of 50 J/cm<sup>2</sup>)</p> <p>Sham PDT consists of an infusion of dextrose 5% solution followed by light application PDT</p>
<b>Efficacy assessments</b>	<ul style="list-style-type: none"> <li>• Best Corrected Visual Acuity assessment</li> <li>• Indocyanine Green Angiography</li> <li>• Fluorescein Angiography and Color Fundus photography</li> <li>• Optical Coherence Tomography</li> </ul>
<b>Safety assessments</b>	<ul style="list-style-type: none"> <li>• Vital signs</li> <li>• Ophthalmic examination</li> </ul>
<b>Other assessments</b>	<ul style="list-style-type: none"> <li>• Health-related Quality of Life (VFQ-25, IVI scale)</li> </ul>
<b>Data analysis</b>	<p>The Full Analysis Set (FAS) comprises all patients to whom treatment regimen has been assigned. Following the intent-to-treat principle, patients will be analyzed according to the treatment regimen they are assigned to at randomization. No data will be excluded from the FAS analyses because of protocol deviations.</p> <p>The primary variables are the BCVA change at Month 12 compared to baseline and the occurrence of complete polyp regression at Month 12. The primary analysis will be performed on the FAS using the LOCF approach for imputing missing data.</p> <p>The primary objective of this trial is to show in a first step, that combination treatment (verteporfin + ranibizumab) is non-inferior to ranibizumab monotherapy with respect to the BCVA change from baseline at Month 12 and that combination treatment is superior with respect to occurrence of complete polyp regression at Month 12.</p> <p>The following hypotheses will be tested at a one-sided 0.025 level.</p> <p>Non-inferiority with respect to BCVA:  <math>H01: \mu_{\text{combination}} - \mu_{\text{mono}} \leq -\Delta</math> versus <math>HA1: \mu_{\text{combination}} - \mu_{\text{mono}} &gt; -\Delta</math></p> <p>Superiority with respect to complete polyp regression:  <math>H02: p_{\text{combination}} - p_{\text{mono}} \leq 0</math> versus <math>HA2: p_{\text{combination}} - p_{\text{mono}} &gt; 0</math></p> <p>Where <math>\mu_{\text{combination}}</math> and <math>\mu_{\text{mono}}</math> are the unknown mean changes from baseline in BCVA at month 12 in the combination therapy and monotherapy and where <math>p_{\text{combination}}</math> and <math>p_{\text{mono}}</math> are the unknown proportions the combination therapy and monotherapy, respectively. <math>\Delta</math> is the non-inferiority margin and is pre-defined to be 5 letters. The hypothesis testing with respect to non-</p>

	<p>inferiority of BCVA will be carried out using an analysis of covariance model including treatment group as factor and baseline BCVA as continuous variable. The Fisher-test will be performed to test for superiority with respect to complete polyp regression.</p> <p>After establishing non-inferiority of BCVA and superiority with respect to complete polyp regression in a second step superiority of BCVA with respect to the BCVA change from baseline to Month 12 will be tested at the one sided level of <math>\alpha = 0.025</math>.</p> <p>Superiority with respect to BCVA:</p> <p>H03: <math>\mu_{\text{combination}} - \mu_{\text{mono}} \leq 0</math> versus HA3: <math>\mu_{\text{combination}} - \mu_{\text{mono}} &gt; 0</math></p> <p>The hypothesis testing with respect to superiority of BCVA will be carried out using an analysis of covariance model including treatment group as factor and baseline BCVA as continuous variable.</p> <p>With this testing strategy the overall alpha (family-wise error rate) will be kept at the one-sided <math>\alpha</math>-level of 0.025.</p>
<b>Key words</b>	Polypoidal choroidal vasculopathy; visual acuity; ranibizumab; verteporfin PDT

## 1 Introduction

### 1.1 Background

Neovascular or wet age-related macular degeneration (AMD) is a leading cause of legal blindness in elderly patients in developed countries. The disease is characterized by classic and occult choroidal neovascularization (CNV) which is classified by fluorescein angiography (FA). Occult CNV involves abnormalities beneath the retinal pigment epithelium (RPE) less clearly visualized with FA. Imaging with indocyanine green angiography (ICGA) has provided more information in these deeper layers, particularly the choroidal circulation and its abnormalities. Using ICGA, polypoidal choroidal vasculopathy (PCV) characterized by a distinctive appearance of a branching vascular network (BVN) representing the typical form of wet AMD and terminal polypoidal dilatations was identified (Maruko et al 2007, Spaide et al 1995, Yannuzzi et al 1997, Yannuzzi et al 1999, Ciardella et al 2004). The polypoidal lesions originate from the inner choroidal vasculature and can progress beneath the RPE (Yannuzzi et al 1997, Uyama et al 2002, Yuzawa et al 2005). The presence of orange-red nodule like structures beneath the RPE associated with an adjacent serous pigment epithelial detachment, or overlying neurosensory detachment, subretinal hemorrhage and lipid exudates is considered the clinical hallmark of PCV. It is difficult to distinguish PCV from other subtypes of occult wet AMD based on only FA (Yannuzzi et al 1997), thus ICGA is critical in making the diagnosis of PCV.

PCV is prevalent in 10-54% of Asian patients, and in 8-12% of Caucasian patients with presumed exudative AMD (Kwok et al 2002, Sho et al 2003, Obata et al 2006, Chen et al 2008). The pathogenesis is not fully understood. The visual prognosis in PCV has been reported to be better than that of exudative AMD; although subretinal fibrosis and RPE atrophy can cause significant and permanent vision loss in PCV (Shiraga et al 1999). Moreover, the incidence of sub-RPE hemorrhage or subretinal hemorrhage in patients with PCV is high (30-64%) (Sho et al 2003, Yoon et al 2007). In a study of the natural history of patients with PCV (Uyama et al 2002) it was reported that half of the study eyes had hemorrhagic episodes, recurrent leakage, or severe RPE atrophy after a long follow-up period (24-54 months). Eyes with a cluster of grape-like polypoidal dilations of the vessels were suggested to be at higher risk of severe visual loss.

Usually only patients with macular involved PCV are treated, unless central vision is threatened by persistent or progressive exudation from non-macular involved PCV. Direct laser photocoagulation can be used for extrafoveal PCV. For active and symptomatic PCV with subfoveal lesions, clinical experience and preliminary data show that photodynamic therapy (PDT) with verteporfin may result in complete regression of polyps and stable or improved vision can be achieved in 81-100% of PCV patients after one year (Chan et al 2004, Gomi et al 2008a).

Patients with PCV have been reported to have higher concentrations of vascular endothelial growth factor (VEGF) in the aqueous humor compared with those of AMD (Tong et al 2006). Histopathologic examination also suggested an association between VEGF expression and PCV (Matsuoka et al 2004).

Ranibizumab monotherapy and the combination of ranibizumab and verteporfin PDT are the most common treatment modalities for symptomatic macular PCV with satisfactory visual outcomes (reviewed by [Lim et al 2010](#), [Laude et al 2010](#), [Imamura et al 2010](#)).

The efficacy and safety of ranibizumab in patients with wet AMD has been widely documented [Ranibizumab IB]. Emerging evidence has shown that PCV responds well to anti-VEGF monotherapy, resulting in rapid resolution of retinal thickening and exudate accumulation, and improvement in vision ([Gomi et al 2008b](#), [Reche-Frutos et al 2008](#), [Ghajarnia et al 2007](#), [Kokame et al 2010](#), [Lee et al 2008](#), [Song et al 2009](#), [Saito et al 2011](#), [Cho et al 2012](#), [Hikichi et al 2012](#), [Koh et al 2012](#)). However, the PCV complex may still exist after treatment as the majority of polyps remains open and may contribute to the recurrence of PCV ([Gomi et al 2008b](#), [Lai et al 2008](#), [Hikichi et al 2012](#), [Koh et al 2012](#)).

Combination of anti-VEGF therapies such as ranibizumab together with verteporfin PDT aims to achieve synergistic effect by combining phot thrombosis of the polyps with anti-vasoproliferative and anti-permeability therapy in order to maintain vision and reduce recurrence of PCV. The EVEREST study ([Koh et al 2012](#)) was the first randomized, active controlled trial in patients with symptomatic macular PCV to assess treatment outcome with verteporfin PDT either alone or in combination with ranibizumab and ranibizumab monotherapy using re-treatment criteria primarily based on polyp regression assessed by ICGA. In this 61 patients and 6 months study, verteporfin PDT combined with ranibizumab or verteporfin monotherapy was statistically superior to ranibizumab monotherapy in achieving complete polyp regression. All three treatment groups showed VA gain over 6 months.

Verteporfin PDT standalone has also been used in clinical practice to treat symptomatic macular PCV ([Chan et al 2004](#), [Silva et al 2005](#), [Mauget-Faysse et al 2006](#), [Otani et al 2007](#), [Gomi et al 2008a](#), [Koh et al 2012](#)). However, the visual outcomes of verteporfin PDT are inferior to ranibizumab in wet AMD trials ([Brown et al 2006](#)).

Both ranibizumab and verteporfin PDT are approved treatments for wet AMD. The present study will investigate the long term therapeutic effects of ranibizumab as monotherapy or in combination with verteporfin PDT in patients with symptomatic macular PCV.

## 1.2 Purpose

The purpose of this study is to compare the effect of ranibizumab administered as monotherapy vs. ranibizumab administered in combination with verteporfin PDT on visual acuity in patients with symptomatic macular PCV with treatment guided by predefined retreatment criteria. In addition, the study will explore potential correlations between retinal anatomical features and visual acuity. The results of this study will provide long-term safety and efficacy data used to generate further guidance on the management of patients with PCV.

### Research Hypothesis:

The underlying research hypothesis is that improvements of anatomical outcomes upon treatment with ranibizumab in combination with verteporfin PDT, specifically complete polyp regression, will result in equal or better vision compared to ranibizumab monotherapy.

## 2 Study Objectives

### 2.1 Primary objectives

The primary objectives will be evaluated in the study eye.

The primary objective is to demonstrate that ranibizumab combined with verteporfin PDT is non-inferior to ranibizumab monotherapy in patients with symptomatic macular PCV as assessed by the change in best corrected visual acuity (BCVA) from baseline to Month 12 and superior with respect to complete polyp regression assessed by ICGA at Month 12. If this is established, the next step will be to demonstrate that ranibizumab combined with verteporfin PDT is superior to ranibizumab monotherapy as assessed by the change in best corrected visual acuity (BCVA) from baseline to Month 12.

### 2.2 Secondary objectives

All secondary efficacy objectives will be evaluated in the study eye:

1. To evaluate the change from baseline in BCVA over time up to Month 24.
2. To evaluate the proportion of patients with  $\geq 5$ ,  $\geq 10$ , and  $\geq 15$  letter increase in BCVA from baseline up to Month 24.
3. To evaluate the proportion of patients with a BCVA loss of  $< 5$ ,  $< 10$ ,  $< 15$ , and  $< 30$  letters in BCVA from baseline up to Month 24.
4. To evaluate the proportion of patients who have maintained their BCVA (within 5 letter change) at Month 12 and 24 compared to the BCVA at the time point of first ranibizumab treatment interruption.
5. To evaluate the change in BCVA at Month 12 and 24 compared to the time point of first ranibizumab treatment interruption.
6. To evaluate the proportion of patients with complete polyp regression as assessed by ICGA at Months 6, and 24.
7. To evaluate the proportion of patients with presence of leakage as assessed by FA at Month 6, 12, and 24.
8. To evaluate the changes in central subfield thickness (CSFT) by SD-OCT from baseline over time.
9. To evaluate the total number of treatments with ranibizumab and verteporfin PDT in the study eye received from baseline up to Month 12 and up to Month 24.
10. To evaluate the number of treatments with ranibizumab in the study eye received from Month 3 up to Month 12 and up to Month 24.
11. To evaluate Vision-related QOL by means of the VFQ-25 assessed at baseline, Months 3, 12, and 24.
12. To evaluate safety and tolerability up to Month 12 and Month 24.



## **2.3 Exploratory objectives**

1. To evaluate the changes in the area of BVN by ICGA from baseline to Month 12 and Month 24.
2. To evaluate the proportion of patients who have developed secondary CNV (presence of feeder vessels) or CNV due to wet AMD by ICGA/FA over time up to Month 24.
3. To evaluate the correlation between baseline characteristics and changes in BCVA and CSFT, as well as complete polyp regression over time up to Month 24. Such baseline characteristics include initial BCVA, duration of visual symptoms prior to randomization, size of polyps, and presence of macular hemorrhage.
4. To evaluate SD-OCT and FA/ICGA images as diagnostic tools in PCV.
5. To evaluate the flow dynamics of the PCV lesion in ICGA, including time of “dye appearance in BVN and polyps”.
6. To explore the safety in patients undergoing bilateral treatment with ranibizumab.
7. To evaluate impairment by means of the Impact of Vision Impairment scale assessed at baseline, Months 3, 12, and 24.

## **3 Investigational plan**

### **3.1 Study design**

This study will use a two-arm, parallel-group, randomized, double-masked design.

There will be 4 periods in this study: the Screening Period, Treatment Period 1, Treatment Period 2, and the Post-treatment Follow-up Period (see [Figure 3-1](#)). The overall study duration for each patient will be 24 months.

#### **Screening Period: Day –14 to Day –1**

At Screening (Visit 1 to occur between Day –14 and Day –4), after signing the informed consent, patients are enrolled into the study and assessment of the study eligibility criteria are to be performed.

#### **Treatment Period 1: Day 1 to Month 11**

Upon confirmation of eligibility, including confirmation of eligibility of the study eye by the Central Reading Center (CRC), patients will be randomized 1:1 to one of two treatment arms, ranibizumab monotherapy or combination therapy with ranibizumab and verteporfin PDT.

All patients will be administered ranibizumab on Day 1 (baseline visit), at Months 1 and 2 (loading phase), and then as needed at intervals of at least one month based on the retreatment criteria algorithm in the remaining maintenance phase (for details see [Section 5.5.6](#)). In addition, patients will also be administered verteporfin PDT (combination group) or sham PDT (ranibizumab monotherapy group) on Day 1 and then as needed from Month 3 through Month 11, at intervals of at least 3 months based on the retreatment criteria algorithm (for details see [Section 5.5.6](#)).

The last possible treatment administration in Treatment Period 1 occurs at Month 11. Visits to assess safety and efficacy are scheduled at monthly intervals. The evaluation of the primary objective will be based on the Month 12 assessments. Following the Month 12 assessments, patients will enter Treatment Period 2.

#### **Treatment Period 2: Month 12 to Month 23**

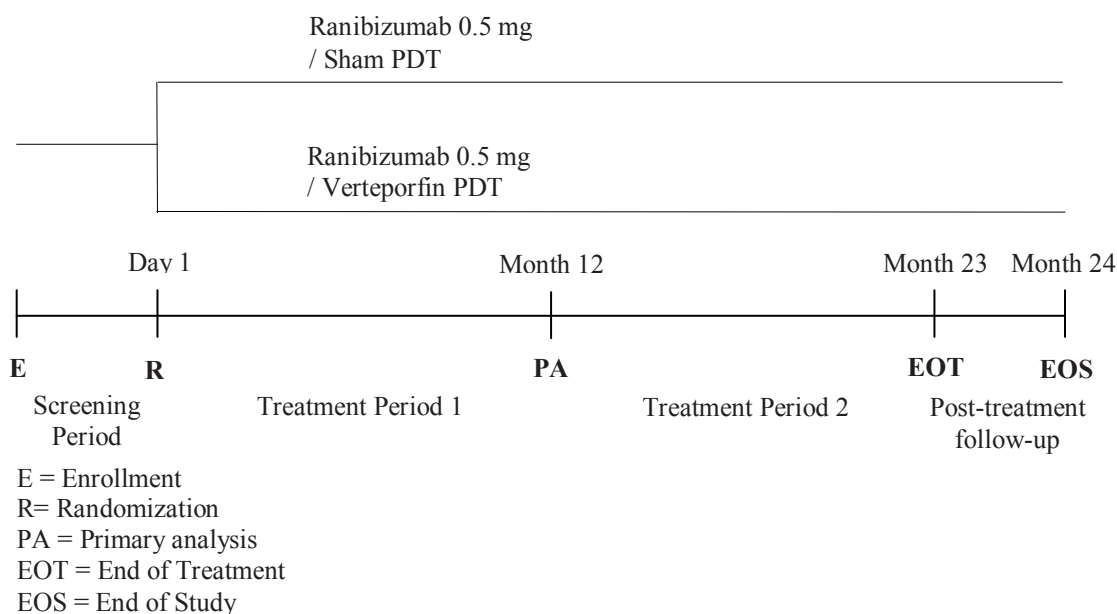
As part of the maintenance phase, patients will continue to be monitored monthly and treated according to the retreatment criteria detailed in [Section 5.5.6](#) until the conclusion of the study. Depending on the results of the primary analysis at Month 12, patients will continue to be treated with the same assigned treatment as in Treatment period 1, or switched to more successful treatment (for details see [Figure 3-2](#)).

The last possible study treatment administration in this study occurs at Month 23 (completion of Treatment Period 2).

#### **Post-treatment Follow-up Period: Month 23 to Month 24**

The last study assessment will be performed at Month 24, i.e. 1 month after the last possible ranibizumab injection/PDT treatment in this study.

**Figure 3-1 Study Design**



### 3.2 Rationale of study design

The study design is chosen based on available scientific publications and guidance from international experts in PCV management. The two treatment arms, ranibizumab monotherapy and the combination of ranibizumab and verteporfin PDT, are the most common treatment modalities in clinical practice for symptomatic macular PCV with satisfactory visual outcomes.

From available published data, vision improvement in anti-VEGF monotherapy is comparable to that of the combination of anti-VEGF and verteporfin PDT (Lai et al 2008, Shima et al 2009, Ruamviboonsuk et al 2010, Koh et al 2012). Therefore, a non-inferiority design will be applied in the current study to assess the primary endpoint - the mean change in BCVA from baseline to Month 12 between ranibizumab monotherapy and ranibizumab in combination with verteporfin PDT. In addition, in order to demonstrate the patient benefit of using combination therapy - the primary objective includes the assessment of polyp regression which may lead to disease stabilization and consequently better vision. Other plausible merits of combination therapy such as reduced number of ranibizumab treatments will be further assessed in the secondary endpoints.

A non-inferiority margin of 5 ETDRS letters will be utilized for statistical analysis in the study. This margin is consistent with that of recent non-inferiority trials in wet AMD comparing visual outcomes among various treatment regimens and represents just 1 line on a visual acuity chart. Historically, treatments for wet AMD with a difference in mean change in visual acuity of 1.2 to 1.4 lines (6 to 7 letters) between active treatment and placebo/sham control have been accepted as sufficiently efficacious to be used in clinical practice and/or approved by the FDA (Anon 1999, Bressler 2001, Gragoudas et al 2004). The non-inferiority margin should be smaller than the difference that separates an efficacious treatment from no

treatment. The observed difference in mean change in visual acuity at 52 weeks between monthly injections of ranibizumab and sham treatment was 17 letters (3.4 lines) in the MARINA study (Rosenfeld et al 2006). A difference of 5 letters would represent approximately 29% of the estimated treatment effect from the MARINA study.

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

The ranibizumab treatment regimen chosen for this trial has taken into account the combination effects of ranibizumab and verteporfin PDT and may therefore deviate in some aspects from the recommendations in the local product labels. The product labels are not identical in all participating countries.

The approved dose of 0.5 mg (50uL of 10mg/mL formulation) ranibizumab for intravitreal injection will be used in this study, which is consistent with all local product labels.

Treatment initiation with monthly dosing of ranibizumab followed by the as-needed treatment regimen in this study is consistent with the product label from most participating countries. The as-needed treatment regimen of ranibizumab with monthly monitoring of VA and/or OCT is supported by a wealth of scientific evidence. The PrONTO trial (Lalwani et al 2009) and lately the CATT trial (Martin et al 2011, Martin et al 2012) demonstrated that an OCT-guided dosing regimen with ranibizumab resulted in VA outcomes comparable to those achieved in the pivotal trials with monthly dosing, while averaging substantially fewer injections over the 2-year duration of the study. The retreatment algorithm used in this study (Section 5.5.6) involves additional assessments (FA, ICGA) in order to evaluate the need for treatment with verteporfin PDT (see below).

The approved dose and regimen of verteporfin for intravenous infusion (6 mg/m<sup>2</sup>) followed by laser light at a dose rate of 600 mW/cm<sup>2</sup> will be used in accordance with the product label for subfoveal CNV secondary to AMD. As ICGA is critical for the diagnosis and monitoring of PCV, the decision regarding retreatment with verteporfin PDT will be based on ICGA findings in conjunction with VA, OCT and FA (Section 5.5.6).

Lastly, due to the natural history of PCV and the inherent nature of polyp recurrence (Uyama et al 2002, Imamura et al 2010), a 24-month study is required to adequately evaluate the mid- and long-term efficacy and safety of the treatments.

### **3.4 Rationale for choice of comparator**

The active comparator of this study is ranibizumab monotherapy. As described in the background (Section 1.1), growing evidence has demonstrated that anti-VEGF therapies including ranibizumab rapidly reduce macular thickness and improve vision in PCV by on average 2-3 lines. The available efficacy data on ranibizumab in the treatment of PCV, together with its known long-term safety data in other retinal diseases such as wet AMD and diabetic macular edema (DME) (Singer et al 2012, Eldem 2012, Elman et al 2011, Nguyen et al 2012), warrant the selection of ranibizumab monotherapy as the active comparator in the current study.

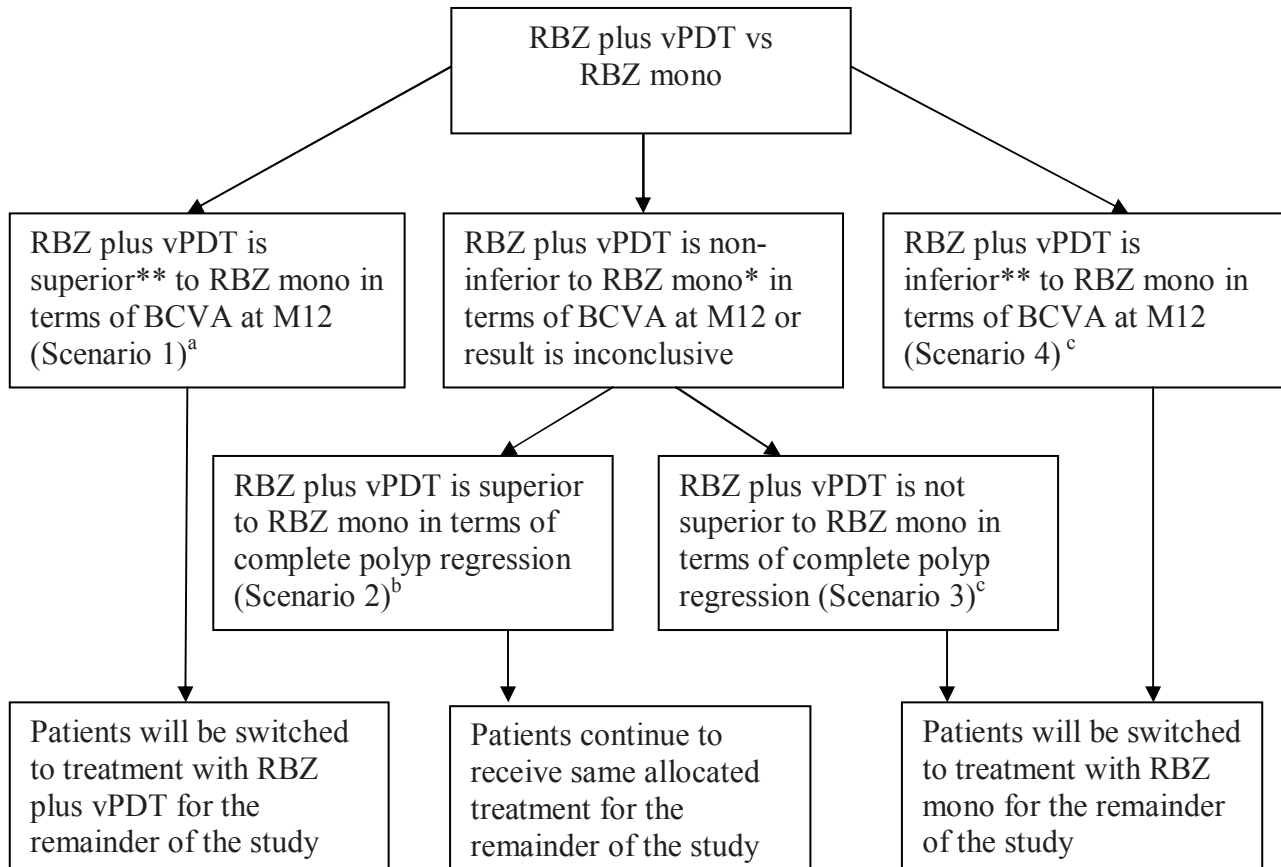
Monotherapy of verteporfin PDT has also been used to treat PCV and has shown 1-year avoidance of moderate visual loss of more than 80% and three-line visual improvement of 25-

55% of the PCV patients (Chan et al 2004, Silva et al 2005, Mauget-Faysse et al 2006, Otani et al 2007, Gomi et al 2008a, Koh et al 2012). However, due to its inferior result in vision improvement in wet AMD, verteporfin PDT cannot be served as the best available active comparator.

### **3.5 Purpose and timing of interim analyses/design adaptations**

An interim analysis will not be performed; however, there will be 2 full analyses. At Month 12, i.e. after all patients have completed Treatment Period 1 (or discontinued the study prior to month 12), the database will be locked and the primary analysis together with all other analyses will be conducted. Depending on the results of the 12 Month analysis, patients will receive the same designated treatment or switched to the more successful treatment regimen. The decision tree for continuation after the Month 12 analysis including the four possible outcome scenarios is outlined in [Figure 3-2](#). A second analysis will occur at Month 24 after the final database lock.

**Figure 3-2 Decision tree for continuation after the Month 12 analysis**



RBZ mono: Ranibizumab monotherapy

vPDT: Verteporfin PDT

M12: Month 12

BCVA: Best Corrected Visual Acuity

<sup>a</sup>: Study objectives met, patients will be switched to the more successful treatment (combination therapy)

<sup>b</sup>: Study objectives partially met, study will continue to monitor benefits of poly regression in Year 2

<sup>c</sup>: Study objectives not met; patients will be switched to the comparator/reference arm (ranibizumab monotherapy)

\*including the cases where the 95% confidence interval of the treatment difference of ranibizumab plus verteporfin PDT versus ranibizumab monotherapy is contained in (-5,0) (ranibizumab plus verteporfin PDT is non-inferior and inferior to ranibizumab monotherapy at the same time) or in (0,5) (ranibizumab monotherapy is inferior and non-inferior to ranibizumab plus verteporfin PDT).

\*\*excluding the cases specified in \*

### 3.6 Risks and benefits

Both ranibizumab and verteporfin have been studied extensively in patients with wet AMD and have a favorable benefit /risk profile (Brown et al 2006, Rosenfeld et al 2006, Bressler et al 2001). The use of the two agents in combination has also been studied in the broad wet AMD patient population where new risks were not identified (Kaiser et al 2012, Larsen et al

2012) and more specifically in patients with the PCV subtype of wet AMD in which combination treatment was associated with favorable outcomes (Koh et al 2012).

Both agents will be used in accordance with their licensed indications and dosing regimens therefore no new risks are anticipated.

As described in the background (Section 1.1), emerging data suggest therapeutic benefits of ranibizumab combined with verteporfin PDT in improving anatomical outcomes, (i.e. polyp regression) while restoring vision in PCV patients. The synergistic effect of ranibizumab and verteporfin PDT may achieve better disease stabilization than ranibizumab monotherapy and therefore, reduce the cost of treatment by decreasing the number of ranibizumab injections.

Being the standard of care for wet AMD, the long-term safety profile of ranibizumab has been well studied in clinical trials and established in real-world clinical practice. As a subpopulation of wet AMD, the demographics of the PCV patients are similar to those of wet AMD with the exception of a higher incidence in Asian ethnic groups. To date, no specific safety risks for PCV have been identified pertaining to ranibizumab treatment.

Verteporfin PDT is another approved therapy for wet AMD. Retinal and vitreous hemorrhages have been reported as side effects of verteporfin PDT in the treatment of Asian patients with wet AMD. These adverse events have been associated with temporary vision impairment (Hirami et al 2007, Ojima et al 2006, Prakash et Han 2006, Yodoi et al 2007). Addition of ranibizumab may reduce the risk of hemorrhage that has been associated with verteporfin PDT via the anti-vascular permeability characteristics of ranibizumab, which may block vascular leakage induced by verteporfin PDT. In summary, the combination of ranibizumab and verteporfin PDT may render additional therapeutic benefits to ranibizumab monotherapy with mitigated risks in ocular safety. The overall risk/benefit ratio for the combination arm is expected to be more favorable than the monotherapy arm of ranibizumab.

## 4 Population

The study population will consist of a group of adults  $\geq 18$  years with symptomatic macular PCV who are naïve to treatment of PCV and CNV due to wet AMD in the study eye. The highest prevalence of PCV has been observed in the Asian population. The anticipated screening failure rate is approximately 20%; therefore, around 400 patients are expected to be enrolled into the study in order to randomize approximately 320 patients. One re-screening of patients who did not meet eligibility criteria is possible as long as recruitment for the study has not been closed yet. Enrollment will be competitive between sites and stopped as soon as the target number of patients has been achieved.

### 4.1 Inclusion criteria

The investigator will assess the eligibility of the patient and the study eye at the screening visit and confirm eligibility prior to randomization. If both eyes are eligible, the eye with the most potential for visual improvement should be selected as determined by the investigator.

The Central Reading Center will confirm the diagnosis of PCV in the study eye based on ICGA and FA imaging prior to randomization.

The Investigator must ensure that all patients who meet the following inclusion criteria are offered participation in the study.

Patients must fulfill all of the following criteria to be eligible for inclusion into this study.

#### Inclusion criteria for patients

1. Written informed consent must be obtained before any assessment is performed
2. Male or Female  $\geq 18$  years of age
3. Willingness and ability to comply with all scheduled visits and study procedures

#### Inclusion criteria for study eye

4. Confirmed diagnosis of symptomatic macular PCV defined by:
  - Active macular polypoidal lesions shown by ICGA AND
  - Presence of serosanguinous maculopathy (i.e. exudative or hemorrhagic features involving the macula on color fundus photography and FA)
5. BCVA letter score between 78-24 (approximately 20/32 to 20/320 Snellen equivalent) using ETDRS visual acuity chart measured at 4 meters
6. Greatest Linear Dimension (GLD) of the total lesion area (BVN + polyyps)  $< 5400 \mu\text{m}$  ( $\sim 9$  MPS Disc Areas) as delineated by ICGA

### 4.2 Exclusion criteria

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



## Exclusion criteria for patient

1. Inability to comply with study or follow-up procedures.
2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
3. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
  - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
  - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
  - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
  - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
  - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

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

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

## Systemic medical history and conditions

4. Any type of systemic disease or its treatment, including any medical condition (controlled or uncontrolled) that over the duration of the study could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk
5. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
6. Stroke or myocardial infarction within the last 3 months prior to Screening
7. Patient with porphyria or history of porphyria

8. Uncontrolled blood pressure defined as systolic value of >160 mm Hg or diastolic value of >100 mm Hg while sitting at Screening or Baseline
9. Known hypersensitivity to:
  - Any of the study drugs (ranibizumab or verteporfin) or any component of their formulations or to drugs of similar chemical classes
  - Fluorescein or indocyanine green

### **Prior or current systemic medication**

10. Use of other investigational drugs within 30 days or 5 half-lives prior to Screening, whichever is longer
11. Previous treatment with systemic anti-VEGF drugs within 6 months prior to Screening (e.g., sorafenib [Nexavar<sup>®</sup>], sunitinib [Sutent<sup>®</sup>], bevacizumab [Avastin<sup>®</sup>])
12. Use of systemic corticosteroids for more than 30 consecutive days during the last 3 months prior to Screening.
13. Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine ([Plaquenil<sup>®</sup>]), tamoxifen, phenothiazines, and ethambutol

### **Ocular medical history and conditions**

#### Study eye

14. Presence of angioid streaks, macular fibrosis, presumed ocular histoplasmosis syndrome, pathologic myopia (evidence of posterior segment abnormalities consistent with pathologic myopia)
15. Tear (rip) of the retinal pigment epithelium involving the fovea at the time of Screening or Baseline
16. Fibrosis or geographic atrophy involving the fovea
17. Active ocular inflammation as well as active or suspected ocular and periocular infections at the time of Screening or Baseline
18. Uncontrolled intraocular hypertension or glaucoma (IOP $\geq$  30 mmHg) despite treatment with anti-glaucoma medication at the time of Screening or Baseline
19. History of rhegmatogenous retinal detachment or macular hole (stage 3 or 4)
20. Ocular disorders in the study eye (e.g. cataract, retinal vascular occlusion, diabetic retinopathy) that, in the opinion of the investigator may confound interpretation of study results or compromise VA or require medical or surgical intervention during the study period
21. Inability to obtain photographs, FAs, ICGAs, or OCTs to document the lesion (e.g. due to media opacity, insufficient pupillary dilation, or lack of venous access)

## **Prior or current ocular treatment**

### Study eye

22. Prior treatment with verteporfin PDT, external-beam radiation, subfoveal or extrafoveal focal laser photocoagulation, submacular surgery, or transpupillary thermotherapy
23. Prior treatment with any anti-VEGF compound or any investigational treatment
24. History of intraocular surgery in the study eye including pars plana vitrectomy and intraocular hemorrhage displacement (e.g. injection of gas with or without tissue plasminogen activator)
25. Cataract surgery within 60 days prior to Screening
26. Prior complicated cataract surgery
27. History of YAG laser posterior capsulotomy in the study eye within 30 days prior to Screening
28. Treatment with intravitreal or subtenon corticosteroid injection or device implantation within 90 days prior to Screening

### Fellow eye

29. Prior treatment with any anti-VEGF compound or any investigational treatment if administered < 90 days before Screening

## 5 Treatment

### 5.1 Protocol requested treatment

#### 5.1.1 Investigational treatment

- Ranibizumab for intravitreal injection, 0.05 mL of 10 mg/mL formulation
- Verteporfin for intravenous infusion ( $6 \text{ mg/m}^2$ ) followed by laser light at a dose rate of  $600 \text{ mW/cm}^2$  delivered for 83 seconds (light dose of  $50 \text{ J/cm}^2$ )
- Sham PDT consists of dextrose 5% solution followed by light application PDT

Ranibizumab solution for injection (labeled as RFB002 0.5mg/0.05mL), corresponding to a 0.5 mg dose) will be supplied as open label bulk supply by Novartis. Vials of ranibizumab are for single use only and the content of the vials must not be split. The vials must be stored in a refrigerator according to the medication label and kept in a secure locked facility. Novartis will provide sufficient supplies of ranibizumab for treatment use to allow for completion of the study.

Verteporfin or sham PDT (dextrose 5% solution) treatment will be supplied locally. Verteporfin must be stored according to the label instructions and kept in a secure locked facility accessible only to unmasked personnel.

#### 5.1.2 Additional study treatment

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

### 5.2 Treatment arms

On Day 1, patients will be assigned in a 1:1 ratio to one of the following two treatment arms:

Ranibizumab monotherapy: Ranibizumab (0.5 mg) plus sham PDT

Ranibizumab combination therapy: Ranibizumab (0.5 mg) plus verteporfin PDT

### 5.3 Treatment assignment

At Visit 2, an eligible patient will be given the lowest available randomization number. This number assigns the patient to one of the treatment arms. The investigator will enter the randomization number on the eCRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

The randomization will be balanced by site.

The randomization scheme for patients will be reviewed and approved by a member of the IIS Randomization Group.

## 5.4 Treatment masking

Since the two study drugs have very different appearances and route of administration, study treatment masking during the study is necessary to minimize the potential for patient and Investigator bias.

Patients, Evaluating Physician Investigators, Vision Examiners, and CRC graders will be masked to the identity of treatment until the 12 months database lock. Masked site personnel responsible for the conduct and monitoring of the study will also be masked to the identity of treatment until Month 12. Depending on the results of the Month 12 analysis, patients will be switched to the more successful treatment in which case Investigators, and patients will become unmasked (see [Figure 3-2](#), Scenarios 1, 3, and 4). If patients continue to receive the same allocated treatment in Year 2 of the trial (see [Figure 3-2](#), Scenario 2), patients, Evaluating Physician Investigators, Vision Examiners, and CRC graders will be masked to the identity of treatment until the final database lock at Month 24.

Sponsor clinical trial personnel involved with the analysis and interpretation of the data will remain masked until Month 12 database lock but will be unmasked thereafter. Aggregated results, summarized by treatment group may be reported to the public before completion of the study.

The Treating Physician, assistants helping with the preparation and administration of the treatment, the local field monitor performing drug reconciliation and review drug accountability will be unmasked.

To fulfill the masking requirements of the study, the following site personnel as outlined in [Table 5-1](#) are required.

**Table 5-1 Required site personnel**

	Masking	Tasks during the study
VA assessor (Vision examiner)	Masked to the treatment assignment	<ul style="list-style-type: none"> <li>performs VA assessment</li> <li>provides the visual acuity result to the evaluating investigator</li> </ul>
Evaluating investigator	Masked to the treatment assignment	<ul style="list-style-type: none"> <li>receives VA result</li> <li>conducts or supervises all remaining assessments (i.e. ophthalmoscopy, OCT, FA, ICGA)</li> <li>provides treatment decision to the treating investigator using formalized communication</li> </ul>
Treating investigator	Unmasked to the treatment assignment	<ul style="list-style-type: none"> <li>performs the treatment – ranibizumab injection/verteporfin PDT/sham PDT</li> <li>must not be involved in other aspects of the study</li> </ul>
Unmasked assistants (limited number – all other support staff should remain masked)	Unmasked to the treatment assignment	<ul style="list-style-type: none"> <li>performs procedure preparations</li> <li>treatment masking (verteporfin)</li> </ul>

The Evaluating Physician will perform the clinical exam and evaluate the VA score, as well as the OCTs, FAs, and ICGAs to determine the need for retreatment and ICGA to determine the size and location of the laser treatment spot. The Treating Physician will administer verteporfin PDT or sham PDT and ranibizumab treatments and due to the differences in the appearance and route of administration of the study drugs, he/she will be unmasked. Therefore and to avoid any bias in the study assessments, the Treating Physician must not be involved in any other aspect of the study nor divulge the patient’s treatment assignment to anyone. Each study site should have a limited number of unmasked assistants assigned for procedure preparation and treatment masking. The Treating Physician and any unmasked assistants will be designated on the site signature log for these roles.

Once assigned, these roles cannot change for the remainder of the study. To maintain the patients’ masking, the Treating Physician and his/her assistants will make certain the patient has no access to the medication or its packaging before, during, and after treatment.

The Vision Examiners must not have access to study patient records and must not elicit historical information from the patient regarding vision or AEs. The Vision Examiners will be given access to prior refraction information, but must not have access to any prior VA results.

## **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 patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). Once assigned to a patient, a patient number will not be reused. If a patient is re-screened, a new number is assigned. If the patient fails to be randomized for any reason, the reason for not being randomized will be entered on the Screening Log (for data to be collected on Screening failures refer to [Section 6.1](#)).

### **5.5.2 Dispensing the investigational treatment**

Each study site will be supplied by Novartis with investigational drugs and with a set of treatment allocation cards for the treating investigator. The treating Investigator will select the investigational drug to dispense to the patient by taking the treatment allocation card with the lowest available randomization number, scratch-off the seal and assign the treatment as indicated on the previously covered part of the treatment allocation card. The unmasked person(s) will document the allocation to ranibizumab monotherapy or ranibizumab/verteporfin PDT combination therapy on a "Randomization/Treatment" log. The log and the treatment allocation card must be stored in a locked cabinet where only unmasked persons will have access to ensure complete masking of the Evaluating Investigator, VA assessor and other masked site staff. When a patient meets the retreatment criteria, the unmasked person(s) will refer to the Randomization/Treatment log for the patient's treatment assignment.

### **5.5.3 Handling of investigational treatment**

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

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for each drug, but no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of investigational drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all used and unused investigational drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

#### **5.5.4 Verteporfin PDT / sham PDT administration**

##### **Procedure room preparation**

When a patient's condition warrants treatment with both verteporfin PDT/sham PDT and ranibizumab, the procedure room for verteporfin PDT/sham PDT will be prepared first.

##### **Pretreatment patient preparation**

The verteporfin/sham (dextrose 5% in water for infusion) intravenous infusion must be administered using standard aseptic techniques. The skin at the infusion site must be disinfected prior to the infusion as per local label.

##### **Verteporfin PDT and sham PDT treatment preparation and administration**

The verteporfin infusion set will be prepared as outlined in the "Dosage and administration" section of the verteporfin (verteporfin for infusion) label.

The sham infusion will be prepared with 5% dextrose in water solution for infusion. A 30 mL volume of this solution is infused intravenously over a 10-minute period to mimic the verteporfin infusion.

During the infusion, the delivery syringe and intravenous line should be wrapped in aluminum foil or alternatively blankets/paravents can be used to mask the identity of treatment.

Fifteen minutes after the start of the infusion (verteporfin or dextrose 5% in water) laser light is applied to the study eye for 83 seconds with the parameters:

- Light dose 50 J/cm<sup>2</sup>
- Light dose rate 600 mW/cm<sup>2</sup>
- Light wavelength 689 nm

##### **Post-treatment care**

Patients who receive verteporfin PDT will become temporarily photosensitive after the infusion. All patients who receive verteporfin PDT/sham PDT should be instructed to avoid direct sunlight for 2 days. Additional information for patients can be found in the "Precautions" section of the verteporfin (verteporfin for injection) label.

#### **5.5.5 Ranibizumab administration**

##### **Pretreatment patient preparation**

Patients should be instructed to self-administer antimicrobial eye drops to the study eye prior to the treatment visit(s) in accordance with local hospital antimicrobial prescribing guidelines. The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis equipment (if required). The periocular skin, eyelid and ocular surface should be disinfected and adequate anesthesia and a broad-spectrum topical microbicide should be administered prior to the intravitreal injection.



### **Ranibizumab preparation and administration**

The Treating Physician prepares the ranibizumab vial for injection. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected. A 5 µm filter needle should be assembled onto a 1 mL syringe. The entire contents of the vial should be withdrawn with the vial in an upright position. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should then be replaced with a sterile needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

The injection needle should be fully inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the center of the globe. The injection volume of 0.05 mL is then delivered slowly. The scleral site should be rotated for subsequent injections.

### **Post-treatment care**

Immediately after the injection, the Treating Physician will check hand motion and light perception and document the results in the eCRF. Intraocular pressure will be measured within 60 minutes after the injection by the Evaluating Physician. Patients should be instructed to self-administer antimicrobial eye drops to the study eye following the administration of ranibizumab in accordance with local hospital antimicrobial prescribing guidelines. Additional information regarding the administration of ranibizumab including precautions can be found in the local label.

### **5.5.6 Treatment regimen for the study eye**

Patients will be monitored at monthly visits over a period of two years (see assessment schedule in [Table 6-1](#) and [Table 6-2](#)) and treated with ranibizumab and/or verteporfin PDT/sham PDT according to the criteria outlined below and in [Figure 5-1](#).

On visits when per treatment algorithm both ranibizumab and verteporfin PDT/sham PDT treatments are required, such as on Day 1, both treatments should be administered on the same day and ranibizumab should be injected at least 1 hour **after** the verteporfin PDT/sham PDT treatment. All reasonable attempts must be made to treat a patient meeting all re-treatment criteria. If the treatment is not administered, the patient must still be scheduled for the next visit according to the protocol.

#### **Ranibizumab:**

Ranibizumab will be administered monthly as an intravitreal injection with a standard dose of 0.5 mg/0.05 mL for 3 consecutive visits (loading phase). In the following maintenance phase, the interval between ranibizumab treatments will be adjusted as appropriate according to the disease activity. The interval between two ranibizumab doses should not be shorter than 28 days.

In the maintenance phase, clinical examinations including visual acuity should be performed on a monthly basis and the necessity of administration of ranibizumab should be evaluated based on the results of examinations and patient condition (refer to [Figure 5-1](#) Retreatment

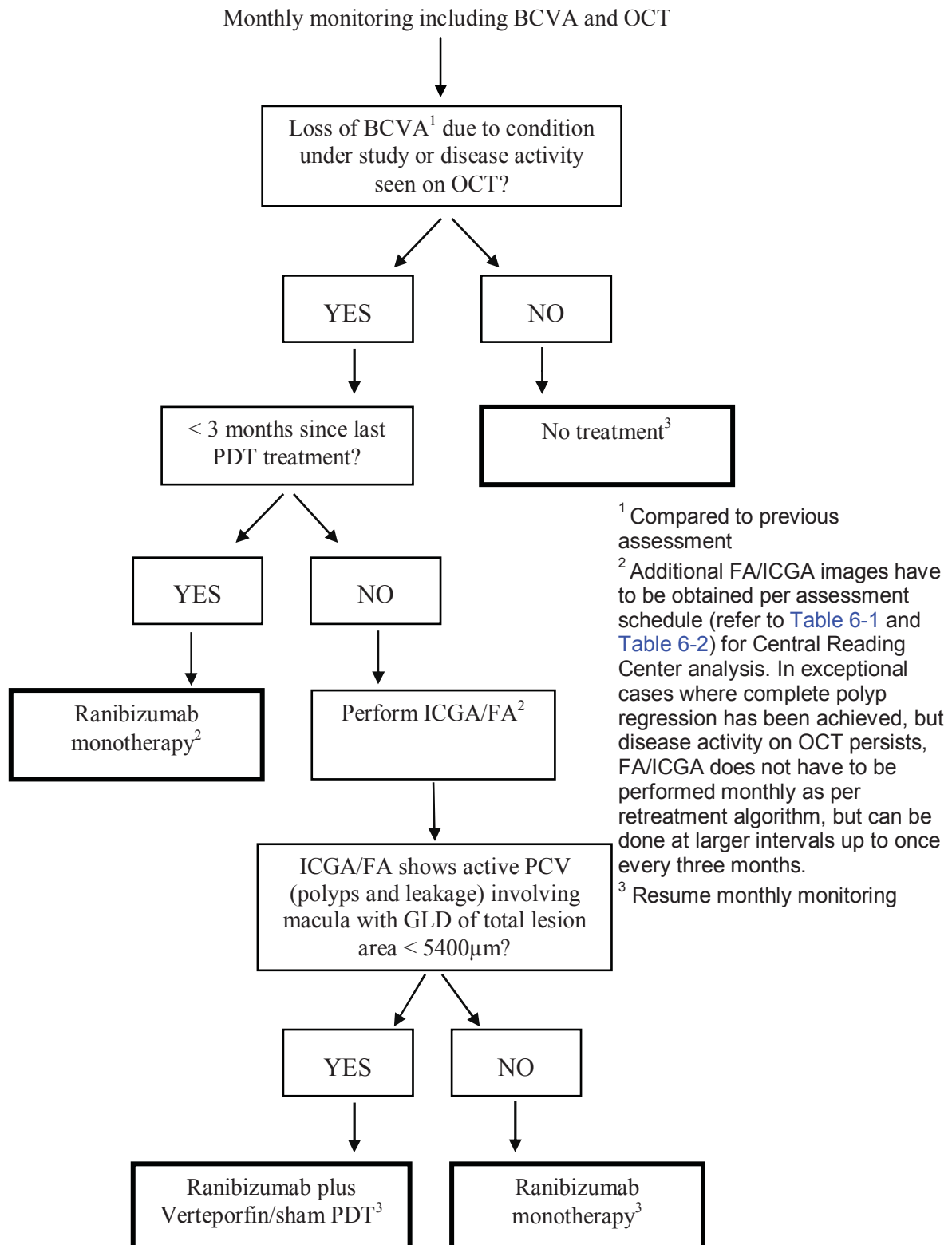
criteria). Efficacy should be regularly assessed, and ranibizumab therapy should not be continued aimlessly if efficacy is no longer observed.

**Verteporfin PDT/sham PDT:**

On day 1, verteporfin PDT/sham PDT is to be administered. Thereafter, patients will be monitored at regular intervals. Verteporfin PDT/sham PDT retreatments are to be administered based on the retreatment criteria algorithm (Figure 5-1). Only one laser spot will be delivered to the macula. At the initial treatment, the laser should cover the entire active lesion (i.e. BVN plus polyps), subsequent treatments may target partial lesions only (e.g. active polyps). Additional information on how to apply the laser can be found the verteporfin label.

Any verteporfin PDT/sham PDT treatment must be administered within 7 days of the ICGA/FA. The interval between two verteporfin/sham PDTs should not be shorter than 3 months.

**Figure 5-1      Retreatment criteria (after loading phase)**



### 5.5.7 Treatment of the fellow eye

Patients, who develop an ocular condition in the fellow eye (non-study eye) during the study and, in the Investigator's opinion, require treatment, may be treated at the Investigator's discretion except for medications explicitly prohibited by the protocol. Should a patient diagnosed with wet AMD (any subtype, including PCV) require and qualify for treatment with ranibizumab, investigational drug (ranibizumab) may be administered at the investigator's discretion based on the local label.

Ranibizumab treatment of the fellow eye will be captured on the eCRF. The fellow eye must be monitored according to routine clinical practice and AE(s) and SAE(s) are captured on the eCRF.

Treatment of the fellow eye with ranibizumab can be performed on the same day as treatment with ranibizumab in the study eye at the discretion of the investigator. However, at **initial treatment**, administration of ranibizumab to both eyes on the same day should be avoided. In case of bilateral treatment on the same day, the study eye should be treated first.

Treatment of the fellow eye with verteporfin PDT is permitted, but it must be obtained from commercial sources. If treatment of the fellow eye is deemed necessary, the treatment should be carried out on a different day at the discretion of the investigator.

### 5.5.8 Permitted dose adjustments and interruptions of study treatment

The dose of the drugs infused or injected at each treatment visit must not be changed.

Treatment interruption is permitted in case of adverse events, in order to keep the patients on study drug. If treatment is interrupted, it should not be resumed earlier than the next scheduled treatment. Please refer to the local ranibizumab and verteporfin PDT labels for additional guidance on withholding treatment.

Any dose interruptions must be recorded on the Dosage Administration Record eCRF.

### 5.5.9 Rescue medication

Not applicable.

### 5.5.10 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after enrolment into the study. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient started the study must be listed on the Concomitant medications/Significant non-drug therapies eCRF (except for routine medications given for ocular procedures required by the protocol, i.e. fluorescein, indocyanine green, topical antibiotic, topical anesthetic, dilating drops).

### 5.5.11 Prohibited treatment

Use of the treatments displayed in [Table 5-2](#) is NOT allowed after screening.

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

- External-beam radiation therapy, focal laser photocoagulation, transpupillary thermotherapy, vitrectomy, submacular surgery, or other surgical interventions for AMD

- Intraocular surgery including cataract surgery and glaucoma filtering surgery
- Intra-/peri-ocular corticosteroids (including sub-Tenon, but excluding topical formulations) and intra-ocular corticosteroid implants (e.g. dexamethasone [Ozurdex<sup>®</sup>], fluocinolone acetonide [Iluvien<sup>®</sup>])

The use of the following medications is not allowed in **either** eye during the entire duration of the study

- Non-study anti-angiogenic drugs (including any anti-VEGF drugs e.g. pegaptanib [Macugen<sup>®</sup>], bevacizumab [Avastin<sup>®</sup>]; aflibercept [Eylea<sup>®</sup>])

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

- Anti-VEGF drugs (e.g. sorafenib [Nexavar<sup>®</sup>], sunitinib [Sutent<sup>®</sup>], bevacizumab [Avastin<sup>®</sup>])
- Medications known to be toxic to the lens, retina or optic nerve including deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazine and ethambutol.

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

**Table 5-2 Prohibited Treatment**

<b>Medication</b>	<b>Action to be taken</b>
External-beam radiation therapy, focal laser photocoagulation, transpupillary thermotherapy, vitrectomy, submacular surgery, or other surgical interventions for AMD - study eye	Discontinue study drug and study
Other anti-VEGF drugs (ocular in either eye or systemic)	Discontinue study drug and study
Intra-/peri-ocular corticosteroids (including sub-Tenon) – study eye	Discontinue study drug and study
Intra-ocular corticosteroid implants – study eye	Discontinue study drug and study
Intraocular surgery – study eye	Withhold study treatment for 28 days prior to and after surgery
Deferoxamine	No action
Chloroquine/hydroxychloroquine	No action
Tamoxifen	No action
Phenothiazines	No action
Ethambutol	No action
Investigational drugs and interventions	Discontinue study drug and study

### **5.5.12 Discontinuation of study treatment and premature patient withdrawal**

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

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion eCRF.

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

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

- Withdrawal of informed consent

- Emergence of the following adverse events:

  - Stage 3 or 4 macular hole (Study eye)

  - Stroke or Transient ischemic attack

  - Rhegmatogenous retinal detachment (Study eye)

- Pregnancy

- Use of prohibited treatment as per [Table 5-2](#).

- Any other protocol deviation that results in a significant risk to the patient's safety

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who permanently discontinue study treatment and start certain prohibited non-study treatments (see [Table 5-2](#)) should be withdrawn from the study and undergo all assessments for the EOS visits as described in [Table 6-1](#) and [Table 6-2](#).

Patients who discontinue study treatment and do not start a prohibited medication per [Table 5-2](#) should NOT be considered withdrawn from the study. A Study Drug Discontinuation form should be completed, giving the date and primary reason for stopping study treatment. Refer to [Section 6](#) for the required monthly assessments for these patients after discontinuation of study treatment.

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

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

### **5.5.13 Emergency unmasking of treatment assignment**

Emergency unmasking should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Two complete sets of emergency code break cards are provided to the Novartis Pharma Organization. One set is to be retained by the local Novartis Country Pharma Organization (CPO) and one set is to be distributed to the investigators. All code break cards

must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a masked code break card for each patient, with the details of drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. **The unmasked treatment code should not be recorded on the CRF.** The investigator must also immediately inform the Novartis local monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the code break cards in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study drug name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case emergency unmasking is required at a time when the investigator and backup are unavailable.

An assessment will be done by the appropriate study site personnel and Novartis after an emergency unmasking to assess whether or not study drug should be discontinued for a given patient.

#### **5.5.14 Study completion and post-study treatment**

Patients already in screening should not be enrolled into the study once planned enrollment has been met.

Patient will be considered to have completed the study after the evaluations of Visit 26 (Month 24) have been performed.

The investigator will recommend the appropriate follow-up medical care, if needed, for all patients who are prematurely withdrawn from the study.

#### **5.5.15 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 ECs of the early termination of the trial.

## 6 Visit schedule and assessments

Table 6-1 and Table 6-2 list all of the assessments and procedures to be performed by study visits. All data obtained from these assessments must be supported in the patient's source documentation. Assessments are indicated with an "X" when they need to be performed.

A planned study visit schedule will be established at the time of randomization for all patients. All efforts should be made to adhere to this study visit schedule and deviations from this date should be kept within  $\pm 7$  days window. Treatment may be administered on the day of study visit or if this is not possible within 7 days after the occurrence of the study visit. Assessments may be performed during two different days, with the evaluations taking place no more than 2 working days apart.

Should a deviation from the study visit schedule occur, all efforts should be made to return to the planned visit schedule taking in consideration the restrictions on the minimum treatment interval for both ranibizumab and verteporfin PDT.

Study visits are driven by the need for assessments and treatment of the study eye. Assessment of the treated fellow eye conducted outside the visit scheduled for the study eye will be recorded in the source documents only with the exception of AEs and administration of study drug (for details see Sections 6.4 and 6.5).



**Table 6-1 Assessment schedule for Year 1**

ASSESSMENT	TREATMENT PERIOD 1													
	SCR	BSL												SPC
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Month/Day	Scr	0/1	1	2	3	4	5	6	7	8	9	10	11	12
Days	-14 to -1	1	30	60	90	120	150	180	210	240	270	300	330	360
Visit Window (Days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed Consent	X													
Demography	X													
Inclusion/Exclusion	X	X												
Medical History	X													
Prior/Conc. Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA	X*	X	X	X	X	X	X	X	X	X	X	X	X	X*
Vital Signs <sup>a</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test <sup>b</sup>	X													
Ophthalmic Exams <sup>c</sup>	X*	X	X	X	X	X	X	X	X	X	X	X	X	X*
Tonometry <sup>d</sup>	X*	X	X	X	X	X	X	X	X	X	X	X	X	X*
FA/CF <sup>e</sup>	X*				X	X <sup>f</sup>	X <sup>f</sup>	X	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X*
ICGA <sup>e</sup>	X*				X	X <sup>f</sup>	X <sup>f</sup>	X	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X*
OCT	X*	X	X	X	X	X	X	X	X	X	X	X	X	X*
NEI VFQ-25		X			X									X
IVI scale		X			X									X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ranibizumab		X	X	X	Per retreatment criteria (Figure 5-1)									
Verteporfin/Sham PDT		X			Per retreatment criteria (Figure 5-1)									

SCR = Screening; BSL = Baseline; SPC = Study Phase Completion; BCVA = Best corrected visual acuity

<sup>a</sup> Body Surface Area (BSA) to be calculated to determine verteporfin PDT dose

<sup>b</sup> Serum Pregnancy test: Perform on women of childbearing potential. Additional urine pregnancy tests may be performed during the study at the discretion of the Investigator.

<sup>c</sup> Slit lamp exam and fundus exam performed prior to study drug treatment

<sup>d</sup> Tonometry; in the study eye, tonometry is conducted at every visit; in addition, post-injection IOP is measured after each ranibizumab administration.

<sup>e</sup> If performed as part of the normal routine practice (e. g. diagnostic procedures) within 14 days prior to randomization, these can be accepted as pre-treatment values if they comply with requirements described in this protocol and the [CRC Operations Manual].

<sup>f</sup> FA and ICGA only to be performed if required per retreatment algorithm; in exceptional cases where complete polyp regression has been achieved, but disease activity on OCT persists, FA/ICGA does not have to be performed monthly as per retreatment algorithm, but can be done at larger intervals up to once every three months.

\* Assessment to be performed in both the study eye and the fellow eye.

**Table 6-2 Assessment schedule for Year 2**

ASSESSMENT	TREATMENT PERIOD 2											FU
												EOT
Visit	15	16	17	18	19	20	21	22	23	24	25	26
Month/Day	13	14	15	16	17	18	19	20	21	22	23	24
Days	390	420	450	480	510	540	570	600	630	660	690	720
Visit Window (Days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed Consent												
Demography												
Inclusion/Exclusion												
Medical History												
Prior/Conc. Medication	X	X	X	X	X	X	X	X	X	X	X	X
BCVA	X	X	X	X	X	X	X	X	X	X	X	X*
Vital Signs <sup>a</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test <sup>b</sup>												
Ophthalmic Exams <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X*
Tonometry <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X*
FA/CF	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X*
ICGA	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X*
OCT	X	X	X	X	X	X	X	X	X	X	X	X*
NEI VFQ-25												X
IVI scale												X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Ranibizumab	Per retreatment criteria (Figure 5-1)											
Verteporfin/Sham PDT	Per retreatment criteria (Figure 5-1)											

EOT = End of Treatment; EOS = End of Study; FU = Post-treatment follow-up; BCVA = Best corrected visual acuity

<sup>a</sup> Body Surface Area (BSA) to be calculated to determine verteporfin PDT dose

<sup>b</sup> Serum Pregnancy test: Perform on women of childbearing potential. Additional urine pregnancy tests may be performed during the study at the discretion of the Investigator.

<sup>c</sup> Slit lamp exam and fundus exam performed prior to study drug treatment

<sup>d</sup> Tonometry; in the study eye, tonometry is conducted at every visit; in addition, post-injection IOP is measured after each ranibizumab administration.

<sup>f</sup> FA and ICGA only to be performed if required per retreatment algorithm; in exceptional cases where complete polyp regression has been achieved, but disease activity on OCT persists, FA/ICGA does not have to be performed monthly as per retreatment algorithm, but can be done at larger intervals up to once every three months.

\* Assessment to be performed in both the study eye and the fellow eye

## 6.1 Information to be collected on screening failures

Patients who are screened but determined not eligible for treatment are considered screening failures. The reason for this will be documented on the Screening Log. In addition, for all screening failures the date of informed consent, demography information, and SAE data will be collected.

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

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

## 6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all randomized patients as shown in [Table 6-1](#) include:

- Demography: date of birth, gender, childbearing potential, race, ethnicity
- Study eye selection

Other assessments performed at screening to determine eligibility are listed in [Table 6-1](#).

## 6.3 Treatment exposure and compliance

Information regarding study drug administration will be collected on the “Dosage administration record” eCRFs for ranibizumab and verteporfin. Treatment compliance of the study eye will be assessed by comparing the number of doses administered versus the number of doses required according to the re-treatment criteria.

## 6.4 Efficacy

Efficacy assessments will include both functional (BCVA) and anatomical evaluations (ICGA, FA, CF, and OCT). The methods of evaluation and parameters to be assessed are described below.

### Study eye:

The eye meeting the inclusion criteria at screening is the study eye. If both eyes are eligible, the investigator will designate the study eye based on the criteria outlined in [Section 4.1](#). The study eye will be treated and evaluated for efficacy purposes of the study objectives. The assessment schedule is outlined in [Table 6-1](#) and [Table 6-2](#) and all results will be captured in the eCRF.

**Fellow eye:**

The fellow eye will be assessed at three time points as outlined in [Table 6-1](#) and [Table 6-2](#) and results will be documented in the eCRF. In addition, if the fellow eye is diagnosed with wet wAMD (any subtype, including PCV) during the course of the study and subsequently treated with study drug (ranibizumab), the fellow eye diagnosis eCRF including a BCVA assessment will have to be completed at the respective visit. Any additional efficacy assessments performed at the discretion of the investigator during the course of the study will be collected in the source documents only.

**6.4.1 Visual acuity assessment**

Best Corrected Visual Acuity (BCVA) will be assessed in a sitting position using ETDRS visual acuity testing charts at an initial testing distance of 4 meters after performing full refraction.

If it is not possible to perform a refraction or visual acuity testing at 4 meters because visual acuity is too poor for the patient to read at least 4 letters on the refraction/visual acuity chart at this distance, the refraction/visual acuity testing should be attempted at 1 meter. Further details on refraction and visual acuity testing are described in the Visual Acuity Protocol included in the Study Operations Manual.

The BCVA score will be calculated using the VA Assessment Worksheet which will be kept in the source data and the BCVA score will be recorded in the eCRF.

**6.4.2 Indocyanine Green Angiography**

ICGA will be performed as indicated in [Table 6-1](#) and [Table 6-2](#).

If ICGA and FA were performed as part of the normal routine clinical practice (e.g. diagnostic procedures) within 14 days prior to randomization, these images can be accepted as pre-treatment assessments if they comply with requirements for ICGA described in this protocol and the CRC Section of the Study Operations Manual.

ICGA is performed to evaluate the choroidal vasculature and the adjacent layer of the retina, including the presence or absence of polyp(s), the branching vascular network, and leakage. The information will be captured on the CRF.

**Total lesion area:**

The total lesion area is the area of all visible typical nodular hyperfluorescence (polyps) by ICGA together with BVN.

The outline of total lesion area is used to determine the greatest linear dimension (GLD) for applying the laser spot size to the retina when verteporfin PDT is to be administered. The GLD will be reported in the eCRF by the investigator. At the initial treatment, the laser should cover the entire active lesion (i.e. BVN plus polyps), subsequent treatments may target partial lesions only (e.g. active polyps).

**Requirement specification for ICGA:**

Please refer to the CRC section of the Study Operations Manual for equipment specifications and instructions with regards to pre ICGA procedures, CSLO-ICG settings, CSLO-ICG image sequencing, post-capture processing and instructions for upload of images.

#### **6.4.3 Fluorescein Angiography and Color Fundus photography**

Fluorescein angiography (FA) will be performed after color fundus (CF) photography as shown in [Table 6-1](#) and [Table 6-2](#) to assess the choroid and retinal vasculature. Presence or absence of macular edema, leakage, neovascularization, and non-perfusion will be reported on the eCRF. Refer to the CRC section of the Study Operations Manual for further procedural details.

#### **6.4.4 Optical Coherence Tomography**

Optical Coherence Tomography (OCT) images are to be obtained using Spectral Domain (SD) optical coherence tomography (OCT) equipment. For consistency of the OCT data collected, the same HD/SD-OCT device must be used for an individual patient throughout the study.

The investigator must obtain OCT data at visits indicated in [Table 6-1](#) and [Table 6-2](#). The information collected will be used by the investigator to assess the status of disease activity and recorded on the eCRF.

To fully evaluate retinal details, and to monitor the effects of treatment on the lesion, the investigator must use the high resolution scans to obtain the required OCT data. Refer to the CRC section of the Study Operations Manual for further procedural details.

#### **6.4.5 Central Reading Center**

ICGA, FA, and OCT images as well as CF photographs collected at screening, Months 3, 6, 12, and 24 will be sent to the study Central Reading Center (CRC) by the study sites.

Eligibility of the study eye will be confirmed by the CRC by assessment of ICGA and CF images prior to randomization.

In addition, angiographic, photographic and OCT characteristics of the patients' lesions scans will be assessed retrospectively by the CRC Months 3, 6, 12, and 24 (EOS).

The patient's identity will be masked on color fundus photographs, FA and ICGA, and OCT images forwarded to the CRC during the study. Technicians or photographers obtaining the ICGAs, FAs, CFs, and OCTs will undergo certification by the CRC. For details about how to label, store and transfer the images to the CRC, as well as the address, contact person, and telephone/fax numbers, refer to the CRC section of Study Operations Manual.

A digital copy of the CF photographs, ICGA, FA and OCT images will be retained with the source documents at each study center.

#### **6.4.6 Appropriateness of efficacy measurements**

Assessment of BCVA using ETDRS is standard in clinical trials evaluating ophthalmic conditions.

OCT is a non-invasive procedure that uses optical interferometry to visualize the structures within the retina. It is widely used in clinical practice to evaluate the retina in patients with AMD or other retinal diseases.

FA is standard assessment in clinical practice for evaluating the retinal vasculature.

Because PCV lesions originate from the choroidal vasculature and the vascular lesions progress beneath the RPE, there are many clinical and pathologic similarities with AMD. In many cases, it is difficult to distinguish PCV from AMD based on only FA. Since ICG reacts to light with a longer wavelength than fluorescein dye, ICG allows visualization of leaking vessels in the deeper layers of the eye which may not be apparent with FA, thus making ICG-A critical in diagnosing PCV.

## **6.5 Safety**

Safety assessments include the frequency and severity of AEs, vital signs, and ophthalmic examinations. Safety will be assessed at every visit and any AEs will be recorded on the eCRF.

Safety assessments enabling identification of ocular AEs will be conducted at every visit for the study eye and at three time points for the fellow eye as indicated in [Table 6-1](#) and [Table 6-2](#), and recorded in the eCRF. If the fellow eye is treated with study drug, additional safety assessments performed in this eye will be collected in the source documents only.

### **6.5.1 Physical examination**

Not applicable.

### **6.5.2 Vital signs**

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

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

The results will be recorded in the eCRF.

Clinically notable vital signs are defined in [Appendix 1](#).

### **6.5.3 Height and weight**

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at screening and recorded on the eCRF. Prior to the start of each verteporfin PDT treatment, the body weight will be measured again in order to calculate the BSA using a nomogram. This BSA value will be used to determine the verteporfin PDT dose. After screening, the weight and the BSA will be documented in the source documents only.

### **6.5.4 Ophthalmic examinations**

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

Slit lamp and fundus examinations must be performed at every visit in the study eye or both eyes as per [Table 6-1](#) and [6-2](#) and prior to treatment with ranibizumab and verteporfin PDT/sham PDT. Results will be assessed whether they are normal, clinically insignificantly abnormal or clinically significantly abnormal and will be recorded as such in the eCRF. Any clinically significant abnormalities of either eye will be recorded either in the Medical/ocular history eCRF or in the Adverse Event eCRF depending on when the test abnormality occurred.

Tonometry should be conducted at all visits in the study eye and at selected visits in the fellow eye as per [Table 6-1](#) and [Table 6-2](#). Intraocular pressure (IOP) in the study eye will be assessed before, as well as between 15 and 60 minutes after treatment with ranibizumab. The IOP values recorded in mmHg will be entered into the eCRF. In addition, as part of the post-injection safety assessments, perfusion of the optic nerve will be confirmed, and level of vision (including finger counting, hand motion and light perception, if indicated) will be assessed after each injection in the study eye. The results will be recorded in the eCRF.

#### **6.5.5 Laboratory evaluations**

Not applicable

#### **6.5.6 Electrocardiogram (ECG)**

Not applicable

#### **6.5.7 Pregnancy and assessments of fertility**

A serum pregnancy test will be performed by the local laboratory as shown in [Table 6-1](#) for all female patients  $\leq 50$  years and women of child-bearing potential.

#### **6.5.8 Appropriateness of safety measurements**

The safety assessments selected are standard for this patient population.

### **6.6 Other assessments**

#### **6.6.1 Health-related Quality of Life**

##### **National Eye Institute Visual Functioning Questionnaire -25 Items**

HRQoL of patients enrolled in the study will be described with the National Eye Institute Visual Functioning Questionnaire -25 Items (NEI VFQ-25). 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. It has been translated into many languages, which is important for the global nature of this study. The NEI-VFQ-25 consists of 25 items combined into 11 subscales: general vision, ocular pain, near activities, distance activities, driving, color vision, peripheral vision and vision-specific social functioning, mental health, role difficulties and dependency. A single-item general health rating also is included (26<sup>th</sup> item).

Each item of the NEI-VFQ-25 is converted into a 0-100 scale; thus, the lowest and highest possible score are set at 0 and 100 points. Higher scores represent better functioning, and

scores decrease with worsening visual acuity. Results are reported by an overall composite and by individual subscale scores.

The NEI VFQ-25 will be collected at baseline and at months 3, 12, and 24. Given the visual impairment of patients, the form will be collected at the time of the clinic visit as an interviewer-administered format. Interviewers will require approximately 10 minutes for completing this form. A detailed instruction manual relating to the administration and completion procedures for the NEI VFQ-25 will be provided to the sites. Effort should be made to ensure complete and accurate completion of the measure prior to the patient leaving the clinic. Questionnaires will be provided in local languages, where available.

### **Impact of Vision Impairment scale**

A second questionnaire, the Impact of Vision Impairment (IVI) scale, will be administered to patients to assess the impact and association of age-related macular degeneration with participation in daily activities.

The IVI is a 32-item questionnaire developed to measure the impact of vision impairment on restriction of participation in daily activities in five domains of functioning (Weih et al 2002, Lamoureux et al 2006). Each item is rated on a six-level scale from “no difficulty” to “can’t do because of vision”. The IVI demonstrates acceptable reliability over a short period and yields consistent results between interviewers. It has been developed using Rasch measurement to confirm the criterion validity of the instrument (Lamoureux et al 2006). Scoring of the IVI is conducted using a Rasch-based conversion table to a 0-100 range where higher scores reflect better functioning (Lamoureux et al 2006).

The IVI will be collected at baseline and at Months 3, 12, and 24, just after completion of the NEI VFQ-25. The IVI will be interviewer-administered. It requires approximately 10 minutes completing the questionnaire. Questionnaires will be provided in local languages, where available.



## 7 Safety monitoring

### 7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign, symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

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

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

- severity (mild, moderate, severe)
- site (non-ocular, left eye, right eye, both eyes)
- its relationship to the study drug(s) or the ocular injection (suspected/not suspected)
- its duration (start and end dates or if continuing at final exam)
- whether it constitutes a serious adverse event (SAE)
- action taken

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

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

hospitalization is for;

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

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

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see [Section 7.2](#).**

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

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

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

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

## **7.2 Serious adverse event reporting**

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

### **7.3 Pregnancy reporting**

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

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

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

## **7.4 Data Monitoring Committee**

Not applicable.

## **8 Data review and database management**

### **8.1 Site monitoring**

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

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

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

### **8.2 Data collection**

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After the final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

### **8.3 Data Database management and quality control**

Novartis staff (or CRO working on behalf of Novartis) review 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 Novartis staff that 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, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

OCT, FA, CF, and ICGA images of the study eye from selected visits will be read centrally at the Central Reading Center and the results will be sent electronically to Novartis (or a designated CRO). Reconciliation (patient number, visit name/date) of Reading Center data and the clinical database will be performed.

At Month 12 and at the conclusion of the study, the occurrence of any protocol deviations will be confirmed. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unmasked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

#### **8.4 Data Monitoring Committee**

Not required.

## 9 Data analysis

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

There will be two analyses performed in this study: the first analysis after the Month 12 database lock (including the primary analysis) and the second analysis at Month 24 database lock.

For statistical purposes, baseline will be defined as the last available non-missing value collected just prior to the start of treatment in the study eye. Additional specifications for the treated fellow eye will be added to the statistical analysis plan prior to unmasking as needed.

For patients with screening assessments but who do not enter the treatment period data will only be listed.

For all patients only one eye will be considered as the study eye (treated eye), and only for this eye efficacy analysis will be performed.

Unless otherwise specified, all statistical tests will be two-sided with a 0.05 level of significance, and all confidence intervals will be two-sided with 95% confidence level.

Categorical variables will be presented as the number and percentage of patients in each category. Continuous variables will be summarized using descriptive statistics (e.g. n, mean, standard deviation, median, minimum, and maximum).

Further technical details and discussions of the following statistical considerations will be provided in the Statistical Analysis Plan (SAP).

### 9.1 Analysis sets

The **Randomized set** will consist of all randomized patients, i.e. of all patients to whom a randomization number has been assigned.

The **Full Analysis Set (FAS)** comprises all patients to whom treatment regimen has been assigned. Following the intent-to-treat principle, patients will be analyzed according to the treatment regimen they are assigned to at randomization. No data will be excluded from the FAS analyses because of protocol deviations.

The **Per Protocol Set (PPS)** will consist of all patients in the FAS who followed the treatment regimen as randomized and completed Month 12 without clinically significant protocol deviations.

Clinically significant protocol deviations will be identified and documented prior to the Month 12 database lock.

The **Safety Set** will consist of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment. The statement that a patient had no adverse events also constitutes a safety assessment.

All efficacy evaluations will be carried out on the FAS. The analysis for the primary efficacy evaluation will be carried out on both the FAS and the PP set. All safety evaluations will be carried out on the Safety set. Within the safety set, patients will be analyzed as treated.

## 9.2 Patient demographics and other baseline characteristics

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

Relevant medical history (ocular and non-ocular) and current medical conditions will be tabulated by system organ class and preferred term of the MedDRA dictionary. Separate tables will be provided for ocular (in study eye and fellow eye) and non-ocular histories and conditions. Other relevant baseline information will be listed and summarized as appropriate with descriptive statistics.

Analyses will be based on Randomized set.

## 9.3 Treatments

### 9.3.1 Investigational treatment

Descriptive statistics will be provided for exposure to investigational treatment using the Safety Set. The number of ranibizumab injections will be presented by treatment group in frequency tables by visit and cumulatively for the period prior to Month 12 and prior to Month 24. Application of verteporfin PDT will be summarized similarly for the combination treatment arm.

The number of patients who received bilateral injections of ranibizumab within 7, 14, and 28 days will be summarized.

Further details will be provided in the SAP.

### 9.3.2 Concomitant therapies

The number and percentage of patients taking concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary using the Safety Set. Summaries will be presented over two time periods: therapies received prior to the start of study treatment and therapies received after the start of study treatment.

## 9.4 Analysis of the primary variables

### 9.4.1 Variables

The primary variables are the BCVA change at Month 12 compared to baseline and the occurrence of complete polyp regression at Month 12. The primary analysis will be performed on the FAS using the LOCF approach for imputing missing data (see [Section 9.4.2](#)).

### 9.4.2 Statistical model, hypothesis, and method of analysis

The primary objective of this trial is to show in a first step, that combination treatment (verteporfin + ranibizumab) is non-inferior to ranibizumab monotherapy with respect to the BCVA change from baseline at Month 12 and that combination treatment is superior with respect to occurrence of complete polyp regression at Month 12.

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

Non-inferiority with respect to BCVA:



H01:  $\mu_{\text{combination}} - \mu_{\text{mono}} \leq -\Delta$  versus HA1:  $\mu_{\text{combination}} - \mu_{\text{mono}} > -\Delta$

Superiority with respect to complete polyp regression:

H02:  $p_{\text{combination}} - p_{\text{mono}} \leq 0$  versus HA2:  $p_{\text{combination}} - p_{\text{mono}} > 0$

where  $\mu_{\text{combination}}$  and  $\mu_{\text{mono}}$  are the unknown mean changes from baseline in BCVA at month 12 in the combination therapy and monotherapy and  $p_{\text{combination}}$  and  $p_{\text{mono}}$  are the unknown proportions the combination therapy and monotherapy, respectively.  $\Delta$  is the non-inferiority margin and is pre-defined to be 5 letters (see [Section 3.2](#) for the justification of the margin). The hypothesis testing with respect to non-inferiority of BCVA will be carried out using an analysis of covariance model including treatment group as factor and baseline BCVA as continuous variable. The Fisher-test will be performed to test for superiority with respect to complete polyp regression.

After establishing non-inferiority of BCVA and superiority with respect to complete polyp regression in a second step superiority of BCVA with respect to the BCVA change from baseline to Month 12 will be tested at the one sided level of  $\alpha = 0.025$ .

Superiority with respect to BCVA:

H03:  $\mu_{\text{combination}} - \mu_{\text{mono}} \leq 0$  versus HA3:  $\mu_{\text{combination}} - \mu_{\text{mono}} > 0$

The hypothesis testing with respect to superiority of BCVA will be carried out using an analysis of covariance model including treatment group as factor and baseline BCVA as continuous variable.

With this testing strategy the overall alpha (family-wise error rate) will be kept at the one-sided  $\alpha$ -level of 0.025 ([Maurer et al 1995](#)).

#### 9.4.3 Handling of missing values/censoring/discontinuations

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

#### 9.4.4 Supportive analyses

The primary analysis will be repeated for the PP set using the same model as the one used for the primary analysis. Also, the primary analysis will be done without adjustment for the baseline BCVA and using stratified/unstratified Cochran-Mantel-Haenszel Tests. The strata will be derived from the baseline BCVA value (strata 1; baseline BCVA value < 56 letters, strata 2: baseline BCVA  $\geq$  56 letters).

The change from baseline in BCVA and the occurrence of complete polyp regression at Month 12 will be compared between the two treatments based on the assumption of a “Missing at Random (MAR)” process, i.e. assuming that the statistical behavior of a patient who drops out post-withdrawal is the same as that for a patient remaining in the study and sharing the same covariates and the same measurement history. Details about the models and analyses will be given in the SAP. Any major discrepancies in the results across analyses will be investigated as needed.

## 9.5 Analysis of secondary variables

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

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

For continuous and ordered categorical variables, changes from baseline will be compared between treatment groups using ANOVA/ ANCOVA models (with the baseline covariate)/ T-test and stratified/unstratified Cochran-Mantel-Haenszel Tests. Stratification will follow the approach described for the primary analysis as applicable. Logistic regression will be used for analyses of binary endpoints.

For treatment differences, 95% confidence intervals will be calculated for differences of means (based on ANOVA / ANCOVA models) and differences in proportions.

Difference between parametric and non-parametric analyses will be addressed in further data-driven analysis as appropriate.

### 9.5.1 Efficacy variables

The variables related to the secondary objectives are described below:

1. Change from baseline in BCVA over time up to Month 24.
2. Increase of  $\geq 5$ ,  $\geq 10$ , and  $\geq 15$  letter in BCVA from baseline up to Month 24.
3. Loss of  $< 5$ ,  $< 10$ ,  $< 15$  and  $< 30$  letters in BCVA from baseline up to Month 24.
4. Maintenance of BCVA (within 5 letter change) at Month 12 and 24 compared to the BCVA at the time point of first ranibizumab treatment interruption.
5. Change in BCVA at Month 12 and 24 compared to the time point of first ranibizumab treatment interruption.
6. Occurrence of complete polyp regression as assessed by ICGA at Months 6, and 24.
7. Presence of leakage as assessed by FA at Month 6, 12, and 24.
8. Changes in central subfield thickness (CSFT) by SD-OCT from baseline over time.
9. Total number of treatments with ranibizumab and verteporfin PDT in the study eye received from baseline up to Month 12 and up to Month 24.
10. The number of treatments with ranibizumab in the study eye received from Month 3 up to Month 12 and up to Month 24.

### 9.5.2 Safety variables

Safety parameters will include adverse events, the results of ophthalmic examinations, intraocular pressure (IOP), and vital signs.

All safety analyses will be conducted within the Safety Set.

#### Adverse Events

Adverse events will be deemed treatment emergent if the onset date is on or after the date of first study treatment. Any adverse events recorded prior to the start of study treatment will be

listed together with all other adverse events. Only treatment-emergent adverse events will be summarized.

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

All the AEs after the first bilateral treatment will be listed with relation to the date of the bilateral treatment (flagged 7, 14 or 28 days after the latest bilateral treatment).

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

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

### **Vital signs and IOP**

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

### **9.5.3 Health-related Quality of Life**

The Visual Function Questionnaire (VFQ-25) and the Impact of Vision Impairment (IVI) scale will be scored at baseline, Months 3, 12 and Month 24. The corresponding absolute scores and the absolute changes will be calculated and summarized descriptively.

## **9.6 Interim analyses**

No interim analyses are planned for this study. However, the primary analysis and all other efficacy and safety analyses will be conducted at the end of Treatment Period 1, i.e. at the time point when all patients still in the study have completed the Month 12 visit. The analysis of the complete study data, including data from both Treatment Periods and the Post-treatment Follow-up Period will be performed when all patients have either completed the post-treatment follow-up or have discontinued the study.

## **9.7 Sample size calculation**

The sample size calculation for the primary analyses is based on the FAS (LOCF) and the following assumptions:

- Proportion of patients with complete polyp regression at Month 12: combination therapy arm: 0.5, ranibizumab monotherapy: 0.2. The assumption is based on clinical feedback. Similar differences of proportions (with higher absolute values) were observed in EVEREST: During the 6-month study EVEREST (Koh et al 2012) the least favorable difference was observed as 0.72 (combination therapy) and 0.33 (ranibizumab monotherapy).
- Change in BCVA from baseline to Month 12:
  - The standard deviation (SD) is 14 letters. Justification: This SD was observed in the study Sustain (patients with wet AMD) (Holz et al 2011). The SD for the BCVA change from baseline to Month 6 in Sustain was comparable to the SD observed in the 6-month study EVEREST (with PCV patients), i.e. this SD is considered as the closest estimate.
  - Treatment difference ( $=\Delta$ ) between combination therapy and ranibizumab monotherapy with respect to the BCVA change from baseline to Month 12. Rather than providing a single assumption for the treatment difference, the sample size /power calculation will be provided for  $\Delta$  equal 0, 1, 2, 3, 4, 5 letters where (e.g.) a  $\Delta = 4$  stands for: The mean change from baseline at Month 12 is 4 letters higher in the combination therapy group compared to ranibizumab monotherapy. Justification: Within the Everest study there exist 2 estimates for the  $\Delta$ : Estimate 1: (Descriptive) Difference of the mean change from baseline at Month 6: 1.7 letters. Estimate 2: Difference based on a model including the baseline BCVA value (i.e. adjusting the treatment effect for baseline BCVA imbalance): 4 letters.
- Data of all patients will be used for the primary analysis through the use of imputation of missing data.

Based on the assumptions above the “marginal” power / sample size for each primary outcome measure is:

- Superiority of the combination therapy vs. ranibizumab monotherapy with respect to the proportion of patients achieving complete polyp regression at Month 12:
  - One sided  $\alpha = 0.0125$ , exact Fisher test: n = 160 patients per arm lead to a power > 0.99

Non-inferiority of the combination therapy vs. ranibizumab monotherapy with respect to the mean BCVA change from baseline at Month 12: Power / sample size scenarios based on n = 160 patients per arm and a non-inferiority margin of 5 letters.

	$\Delta = 5$ letters	$\Delta = 4$ letters	$\Delta = 3$ letters	$\Delta = 2$ letters	$\Delta = 1$ letter	$\Delta = 0$ letters
$\alpha = 0.025$	>0.99	>0.99	>0.99	>0.99	0.96	0.88

(Student’s 2 sample t-test was used assuming equal variances.)

Superiority of the combination therapy vs. ranibizumab monotherapy with respect to the mean BCVA change from baseline at Month 12: Power / sample size scenarios based on n = 160 patients per arm.

	$\Delta = 5$	$\Delta = 4$	$\Delta = 3$	$\Delta = 2$	$\Delta = 1$	$\Delta = 0$

	letters	letters	letters	letters	letter	letters
$\alpha = 0.025$	0.88	0.72	0.48	0.24	0.09	0.025

(Student’s 2 sample t-test was used assuming equal variances.)

Reason for Student’s 2 sample t-test: Based on the Everest data it is expected that the baseline BCVA value will impact the change in BCVA (e.g.) due to ceiling effects. However each arm in the study Everest had only 20 patients which does not allow for a precise estimation of subgroup effects (mean and SD), with subgroups based on baseline BCVA or adding baseline BCVA as a regression effect without further assumptions. Therefore the power is based on the 2 sample situation, while acknowledging that incorporating baseline BCVA information into the statistical model may lead to an increase of power.

The “combined” power (= P (H1and H2,  $\alpha$ )) to achieve non-inferior BCVA and superiority with respect to complete polyp regression at the one-sided level of  $\alpha = 0.025$  is at least

	$\Delta = 5$ letters	$\Delta = 4$ letters	$\Delta = 3$ letters	$\Delta = 2$ letters	$\Delta = 1$ letter	$\Delta = 0$ letters
Power	0.98	0.98	0.98	0.98	0.95	0.87

The calculation is based on the following formula:

- Claim non-inferior BCVA with a p-value below  $\alpha = 0.025$  and superiority with respect to polyp regression with a p-value below  $\alpha = 0.025$ .
- $1 \geq P (H1, \alpha \text{ or } H2, \alpha) = P (H1, \alpha) + P (H2, \alpha) - P (H1, \alpha \text{ and } H2, \alpha)$  and  $P(H1, \alpha \text{ and } H2, \alpha) \geq P(H1, \alpha) + P(H2, \alpha) - 1$ , where e.g.  $P(H1, \alpha)$  denotes the “marginal” power for non-inferior BCVA from above (at the level of  $\alpha$ ).
- Please note, that in case the “marginal” power was  $\geq 0.99$ , the value 0.99 was used for the calculations and that the table includes the lower boundary of the inequality.

The “combined” power (= P (H1and H2 and H3,  $\alpha$ )) to achieve non-inferior BCVA, superiority with respect to complete polyp regression and superior BCVA at the one-sided level of  $\alpha = 0.025$  is at least

	$\Delta = 5$ letters	$\Delta = 4$ letters	$\Delta = 3$ letters	$\Delta = 2$ letters	$\Delta = 1$ letter	$\Delta = 0$ letters
Power, n=160	0.87	0.71	0.47	0.23	0.08	0.015

The calculation is based on the following formula:

$$P (H3, \alpha \text{ and } H2, \alpha) \geq P (H3, \alpha) + P (H2, \alpha) - 1$$

as non-inferiority is implied by superiority of BCVA.

The sample size calculations were performed using nQuery Advisor 7.0.

## **10 Ethical considerations**

### **10.1 Regulatory and ethical compliance**

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

### **10.2 Informed consent procedures**

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

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

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

### **10.3 Responsibilities of the investigator and IRB/IEC**

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. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/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](http://clinicaltrials.gov). In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **11 Protocol adherence**

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

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### **11.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.



## 12 References

Anon (1999) Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group: Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials- TAP Report 1. *Arch Ophthalmol*; 117:1329-45.

Bressler NM (2001) Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials- TAP Report 2. *Arch Ophthalmol*; 119:198-207.

Brown DM, Kaiser PK, Michels M, et al (2006) Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *New Engl J Med*; 355:1432-44.

Chan WM, Lam DS, Lai TY, et al (2004) Photodynamic therapy with verteporfin for symptomatic polypoidal choroidal vasculopathy: one-year results of a prospective case series. *Ophthalmology*; 111:1576-84.

Chen SJ, Cheng CY, Peng KL, et al (2008) Prevalence and associated risk factors of age-related macular degeneration in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Invest Ophthalmol Vis Sci*; 49:3126-33.

Cho HJ, Kim JW, Lee DW, et al (2012) Intravitreal bevacizumab and ranibizumab injections for patients with polypoidal choroidal vasculopathy. *Eye*; 26:426-33.

Ciardella AP, Donsoff IM, Huang SJ, et al (2004) Polypoidal choroidal vasculopathy. *Surv Ophthalmol*; 49(1):25-37.

Eldem B (2012) 2-year safety and efficacy of ranibizumab 0.5 mg in patients with Diabetic Macular Edema (DME): An interim analysis of the RESTORE extension study. COPHyY congress.

Elman MJ, Bressler NM, Qin H, et al (2011) Expanded 2-year follow-up of a trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema [The Diabetic Retinopathy Clinical Research Network, DRCR Network]. *Ophthalmology*; 118:609-14.

Ghajarnia M, Kurup S, Eller A, et al (2007) The therapeutic effects of intravitreal bevacizumab in a patient with recalcitrant idiopathic polypoidal choroidal vasculopathy. *Semin Ophthalmol*; 22:127-31.

Gomi F, Ohji M, Sayanagi K, et al (2008a) One-year outcomes of photodynamic therapy in age-related macular degeneration and polypoidal choroidal vasculopathy in Japanese patients. *Ophthalmology*; 115:141-46.

Gomi F, Sawa M, Sakaguchi H, et al (2008b) Efficacy of intravitreal bevacizumab for polypoidal choroidal vasculopathy. *Br J Ophthalmol*; 92:70-73.

Gragoudas ES, Adamis AP, Cunningham ET Jr, et al (2004) Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med*; 351(27):2805-16.

Hikichi T, Higuchi M, Matsushita T, et al (2012) One-year results of three monthly ranibizumab injections and as-needed reinjections for polypoidal choroidal vasculopathy in Japanese patients. *Am J Ophthalmol*; 154:117-24.

Hirami Y, Tsujikawa A, Otani A, et al (2007) Hemorrhagic complications after photodynamic therapy for polypoidal choroidal vasculopathy. *Retina*; 27:335-41.

Holz FG, Amoaku W, Donate J, et al (2011) Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. *Ophthalmology*; 118(4):663-71.

Imamura Y, Engelbert M, Iida T, et al (2010) Polypoidal choroidal vasculopathy: a review. *Survey of Ophthalmol.* 55;501-15.

Kaiser PK, Boyer DS, Cruess AF, et al (2012) Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study. *Ophthalmology*; 119:1001-10.

Koh A, Lee WK, Chen LJ, et al (2012) EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina*; 32(8):1453-64.

Kokame GT, Yeung L, Lai JC (2010) Continuous anti-VEGF treatment with ranibizumab for polypoidal choroidal vasculopathy: an interim 6-month report. *Br J Ophthalmol*; 94:297-301.

Kwok AK, Lai TY, Chan CW, et al (2002) Polypoidal choroidal vasculopathy in Chinese patients. *Br J Ophthalmol*; 86:892-897.

Lai TY, Chan WM, Liu DT, et al (2008) Intravitreal bevacuzumab (Avastin) with or without photodynamic therapy for the treatment of polypoidal choroidal vasculopathy. *Br J Ophthalmol*; 92:661-66.

Lalwani GA, Rosenfeld PJ, Fung AE, et al (2009) A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol*; 148(1):43-58

Lamoureux EL, Pallant JF, Pesudovs K, et al (2006) Evaluation of Its Measurement Properties using Rasch Analysis. *Invest Ophthalmol Vis Sci.*; 47:4732-4741.

Larsen M, Schmidt-Erfurth U, Lanzetta P, et al (2012) Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results. *Ophthalmology*; 119:992-1000.

Laude A, Cackett PD, Vithana EN, et al (2010) Polypoidal choroidal vasculopathy and neovascular age-related macular degeneration: Same or different disease? *Prog Retina Eye Res*; 29:19-29.

Lee SY, Kim JG, Joe SG, et al (2008) the therapeutic effects of bevacizumab in patients with polypoidal choroidal vasculopathy. *Korean J Ophthalmol*; 22:92-9.

Lim TH, Laude A, Tan CSH (2010) Polypoidal choroidal vasculopathy: an angiographic discussion. *Eye*; 24:483-90.

- Martin DF, Maguire MG, Fine SL, et al (2012) Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: Two-year results. *Ophthalmology*; 119:1388-98.
- Martin DF, Maguire MG, Ying GS, et al (2011) Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*; 364:1897-908.
- Maruko I, Iida T, Saito M, et al (2007) Clinical characteristics of exudative age-related macular degeneration in Japanese patients. *Am J Ophthalmol*; 144:15-22.
- Matsuoka M, Ogata N, Otsuji T, et al (2004). Expression of pigment epithelium derived factor and vascular endothelial growth factor in choroidal neovascular membranes and polypoidal choroidal vasculopathy. *Br J Ophthalmol*; 88(6):809-15.
- Mauget-Faysse M, Quaranta-EL Maftouhi M, De La Marnière E, et al (2006) Photodynamic therapy with verteporfin in the treatment of exudative idiopathic polypoidal choroidal vasculopathy. *Eur J Ophthalmol*; 16(5):695-704.
- Maurer W, Hothorn LA, Lehmacher W (1995) Multiple comparisons in drug clinical trials and preclinical assays (a-priori ordered hypotheses). In: Vollmar J (ed). *Testing Principles in Clinical and Preclinical Trials. Biometrie in der chemisch-pharmazeutischen Industrie 6*. Stuttgart/New York: Gustav Fischer; p. 3–18
- Nguyen QD, Brown DM, Marcus DM, et al (2012) Ranibizumab for diabetic macular edema: Results from 2 Phase III randomized trials: RISE and RIDE. *Ophthalmology*; 119:789-801.
- Obata R, Yanagi Y, Kami J, et al (2006) Polypoidal choroidal vasculopathy and retinchoroidal anastomosis in Japanese patients eligible for photodynamic therapy for exudative age related macular degeneration. *Jpn J Ophthalmol*; 50(4):354–360.
- Ojima Y, Tsujikawa A, Otani A, et al (2006) Recurrent bleeding after photodynamic therapy in polypoidal choroidal vasculopathy. *Am J Ophthalmol*; 141:958-60.
- Otani A, Sasahara M, Yodoi Y, et al (2007) Indocyanine green angiography: guided photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol*; 144:7-14.
- Prakash M, Han DP (2006) Recurrent bullous retinal detachment from photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol*; 142:1079-81.
- Reche-Frutos J, Calvo-Gonzales C, Donate-Lopez J, et al (2008) Short term anatomic effect of ranibizumab for polypoidal choroidal vasculopathy. *Eur J Ophthalmol*; 18:645-8.
- Rosenfeld PJ, Brown DM, Heier J S, et al (2006) Ranibizumab for Neovascular Age-Related Macular Degeneration. *N Engl J Med*; 355:1419-1431.
- Ruamviboonsuk P, Tadarati M, Vanichvaranont S, et al (2010) Photodynamic therapy combined with ranibizumab for polypoidal choroidal vasculopathy: results of a 1-year preliminary study. *Br J Ophthalmol*; 94:1045-51.
- Saito M, Iida T, Kano M (2011) Intravitreal ranibizumab for polypoidal choroidal vasculopathy with recurrent or residual exudation. *Retina*; 31:1589-97.

Shima C, Gomi F, Sawa M, et al (2009) One-year results of combined photodynamic therapy and intravitreal bevacizumab injection for retinal pigment epithelial detachment secondary to age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*; 247:899-906.

Shiraga F, Matsuo T, Yokoe S, et al (1999) Surgical treatment of submacular hemorrhage associated with idiopathic polypoidal choroidal vasculopathy. *Am J Ophthalmol*; 128:147-54.

Sho K, Takahashi K, Yamada H, et al (2003) Polypoidal choroidal vasculopathy: incidence, demographic features, and clinical characteristics. *Arch Ophthalmol*; 121:1392-96.

Silva RM, Figueira J, Cachulo ML, et al (2005) Polypoidal choroidal vasculopathy and photodynamic therapy with verteporfin. *Graefes Arch Clin Exp Ophthalmol*; 243:973-79.

Singer MA, Awh CC, Sadda S, et al (2012) HORIZON: An open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology*; 119:1175-83.

Song JH, Byeon SH, Lee SC, et al (2009) Short-term safety and efficacy of a single intravitreal bevacizumab injection for the management of polypoidal choroidal vasculopathy. *Ophthalmologica*; 223:85-92.

Spaide RF, Yannuzzi LA, Slakter JS, et al (1995) Indocyanine green videoangiography of idiopathic polypoidal choroidal vasculopathy. *Retina*; 15(2):100-10.68

Tong JP, Chan WM, Liu DT, et al (2006) Aqueous humor levels of vascular endothelial growth factor and pigment epithelium-derived factor in polypoidal choroidal vasculopathy and choroidal neovascularization. *Am J Ophthalmol*; 141(3):456-62.

Uyama M, Wada M, Nagai Y, et al (2002) Polypoidal choroidal vasculopathy: natural history. *Am J Ophthalmol*; 133:639-648.

Weih LM, Hassell JB, Keeffe J (2002) Assessment of the Impact of Vision Impairment. *Invest Ophthalmol Vis Sci*; 43:927-935.

Yannuzzi LA, Ciardella A, Spaide RF, et al (1997) The expanding clinical spectrum of idiopathic polypoidal choroidal vasculopathy. *Arch Ophthalmol*; 115:478-485.

Yannuzzi LA, Wong DW, Sforzolini BS, et al (1999) Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. *Arch Ophthalmol*; 117(11):1503-10.

Yodoi Y, Tsujikawa A, Otani A, et al (2007) Chorioretinal anastomosis after photodynamic therapy for polypoidal choroidal vasculopathy: CRA after PDT for PCV. *Int Ophthalmol*; 28:297-9.

Yoon JS, Lee J, Lee SC, et al (2007) Polypoidal choroidal vasculopathy in Korean patients with large submacular hemorrhage. *Yonsei Med J*; 48:225-32.

Yuzawa M, Mori R, Kawamura A (2005) The origins of polypoidal choroidal vasculopathy. *Br J Ophthalmol*; 89:602-607.

### 13 Appendix 1: Clinically notable vital signs

The criteria for clinically notable abnormal vital signs (post baseline) are shown in Table 13-1. In order to be identified as being potentially clinically notable abnormal, an on-treatment vital signs value would need to meet the criterion (column 2), and represent a change of at least the magnitude noted in the change column.

**Table 13-1 Clinically notable abnormal vital signs values for adults**

<b>Variable</b>	<b>Criteria</b>	<b>Change relative to Baseline</b>
Pulse rate	≥120 bpm ≤50 bpm	increase of ≥15 bpm decrease of ≥15 bpm
Systolic blood pressure	≥180 mm Hg ≤90 mm Hg	increase of ≥20 mm Hg decrease of ≥20 mm Hg
Diastolic blood pressure	≥105 mm Hg ≤50 mm Hg	increase of ≥15 mm Hg decrease of ≥15 mm Hg

Clinical Development

Ranibizumab; Lucentis®

Clinical Trial Protocol CRFB002A2412

**A 24-month, phase IV, randomized, double masked, multi-center study of ranibizumab monotherapy or ranibizumab in combination with verteporfin photodynamic therapy on visual outcome in patients with symptomatic macular polypoidal choroidal vasculopathy**

### **Statistical Analysis Plan (SAP)**

Author: Chrystel Feller, Trial Statistician; Philippe Margaron, GMAD;  
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**Document History – Changes compared to previous version of RAP module 3/SAP.**

Version	Date	Changes
Amendment 1		
Draft 0.1	09 Mar 2015	Description on calculation of complete polyp regression added
Draft 0.2	27 Mar 2015	Deleted summary for following CRC parameters: <ul style="list-style-type: none"> <li>• Total Lesion area</li> <li>• Presence of ICG leakage</li> <li>• Presence of macular edema</li> </ul> As PFS information is not collected in CRF, removed summary of ranibizumab with PFS
Draft 1.1	21 Oct 2015	Added secondary objectives 9, 10, 11a, 11b, and 12
Draft 1.2	02 Nov 2015	Re-worded secondary objectives 9, 10, 11, and 12 Defined Month 24 Efficacy Set for Month 24 analysis Removed missing data imputation from secondary analysis Organized baseline variable by categories of FA, OCT, ICGA, etc
Draft 1.3	06 Nov 2015	Added M24 efficacy analysis for FAS Edit MMRM supportive analysis by removing BCVA at month 3 as covariate Re-wording additional analysis
Final	13 Nov 2015	Removed imputation of baseline age information Redefined arms of periods of day 1 to Month 24 Added SAS code
Amendment 2		
Draft 2.1	4 Dec 2015	Table 2-2: “no baseline polyp assessment” leads to PP exclusion LOCF imputation by visit instead of at Month 12 only Update the list of secondary variables VFQ analysis update Typo in SAS Code for Negative Binomial Analysis
Final	25 Jan 2016	Analyses on maintenance of BCVA following first interruption of treatment due to stability removed; add section 2.10 for “change to protocol analyses” BCVA profile over time by baseline fluid mechanics removed; question which should be answered and analysis to be clarified RAP Module 3 Statistical Methodology replaced by Statistical Analysis Plan per new RAP process, RAP module 8 by PDS document Section 2.7.5: note for IVI Summaries for screening failure, demographic and ocular characteristics will be performed for the Month 12 analysis only Section 2.3.5: remove “Post baseline assessments will be included in an analysis for a given anatomical site only if the assessment falls in the study observation period for that site for the given analysis period.” Section 2.3.4: clarify AEs at the cut-off date

Version	Date	Changes
		SAS codes: centered baseline
Amendment 3		
Draft 3.1	2 Feb 2016	Change section 2.3.4 as in G2301
	22 Feb 2016	Add SAS Codes for Kaplan-Meier Table RMP risk: presented without CI (as in the MAP, TREND, G-studies, DRAGON), except that CI presented for the study eye and relative risk
	9 Mar 2016	Section 2.3.5: safety observation period instead of study observation period, definition like in G2301, G2302 Section 2.7.4: AEs excluding SAEs are not of interest Section 2.7.5: flag value with IOP $\geq$ 30 mmHg Centered baseline used in models (ANCOVA, MMRM)
	15 Mar 2016	Correct sas codes
	01 April 2016	Add analysis for IVI with all questionnaires Update imputation rules for KM analysis for flat/fluid-free retina. Table 2-3: correct deviation code descriptions
	13 April 2016	Section 2.8: produce only key efficacy and safety outputs at Month 12 SAS code for CMH Section 2.7.4: add exploratory analyses specified in the protocol Section 2.7.5: add safety exploratory analyses for bilateral trt
	18 April 2016	Table 2-3: add code 4 Table 2-4: visit window for Month 1 Table 2-5: correct possible trt administered Safety observation period instead of study observation period Section 2.6: correct trt pattern example Section 2.6: remove missing site imputation for medication Section 2.7.2: more specific to which endpoint the analyses are performed Flat retina, fluid-free retina: use data from investigator, first occurrence also at Month 24 CSFT change from baseline: summary statistics and time-course plot also with investigator data KM analyses: use data from patients with no occurrence of the event before first treatment Imputation rules for KM plot for disease activity Section: 2.7.4: OCT shift tables and change from baseline at M3, 6 and 12 and not by visit Section 2.7.4: scatterplots by treatment group Section 2.7.6: "translation issue" instead of "issue" Section 2.10: add reference, update arguments SAS code for Clopper-Pearson Exact Binominal CI: correct examples for RESP Correct SAS code for Fisher Add references



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Version	Date	Changes
Final	25 April 2016	Final version
Amendment 4	17 Mai 2016	Update the list of codes leading to exclusion from PPS Clarification for the severity code 4, Table 2-3 SAS code: remove estimate statement in ANCOVA, we use LSMEANS with PDIF only as in MMRM SAS output datasets updated for exact PROC LOGISTIC

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## **1 Statistical methods planned in the protocol and determination of sample size**

This Statistical Analysis Plan (SAP) describes the statistical analysis according to Section 9 of the study protocol and along with any additional analyses, specifications or deviations from this protocol planned before unmasking of the data. Determination of sample size is specified in [Section 2.9](#).

This document is written in the future tense. It will be reviewed and updated (including conversion to past tense) for entry into the clinical study report after the analysis has taken place. The analyses described in this document will be conducted using SAS.

## **2 Statistical and analytical plans**

This study consists of two treatment periods and a post-treatment follow-up period. Treatment Period 1 is from Day 1 to Month 11. Treatment Period 2 is from Month 12 to Month 23. Dosing given PRN and post injection assessments at Month 12 will be considered part of Treatment Period 2. The follow-up period post-treatment is from Month 23 to Month 24.

Unless otherwise stated full statistical analysis described herein will be conducted twice. It will first be performed after the month 12 database lock (DBL) when patients either have completed the Month 12 visit, or have withdrawn from the study prior to completion of the Month 12 visit. This analysis will be considered as the primary analysis. The second analysis takes place at the end of the study after the Month 24 DBL including data from the entire study duration.

Data that is used for the Month 12 analyses but changed after the Month 12 database lock will be reviewed by the team and discussed with respect to the impact on the analyses. This may then result in rerunning certain Month 12 outputs.

After the Month 12 DB lock, the clinical team will be unmasked to treatment; however masking will remain at the investigative sites for the patient and the site personnel.

This SAP will contain specifications for the Month 12 as well as the Month 24 analyses, and may be updated after the Month 12 database lock to address any new issues that become apparent at that time. At Month 24, analyses for assessments which are performed by visit (e.g., visual acuity, vital signs) will include all visits from baseline.

### **Treatment groups for the analysis**

Data will be summarized by treatment group with respect to demographic and baseline disease characteristics, efficacy and safety observations and assessments. The treatment groups for the analysis are specified below for the different analysis periods.

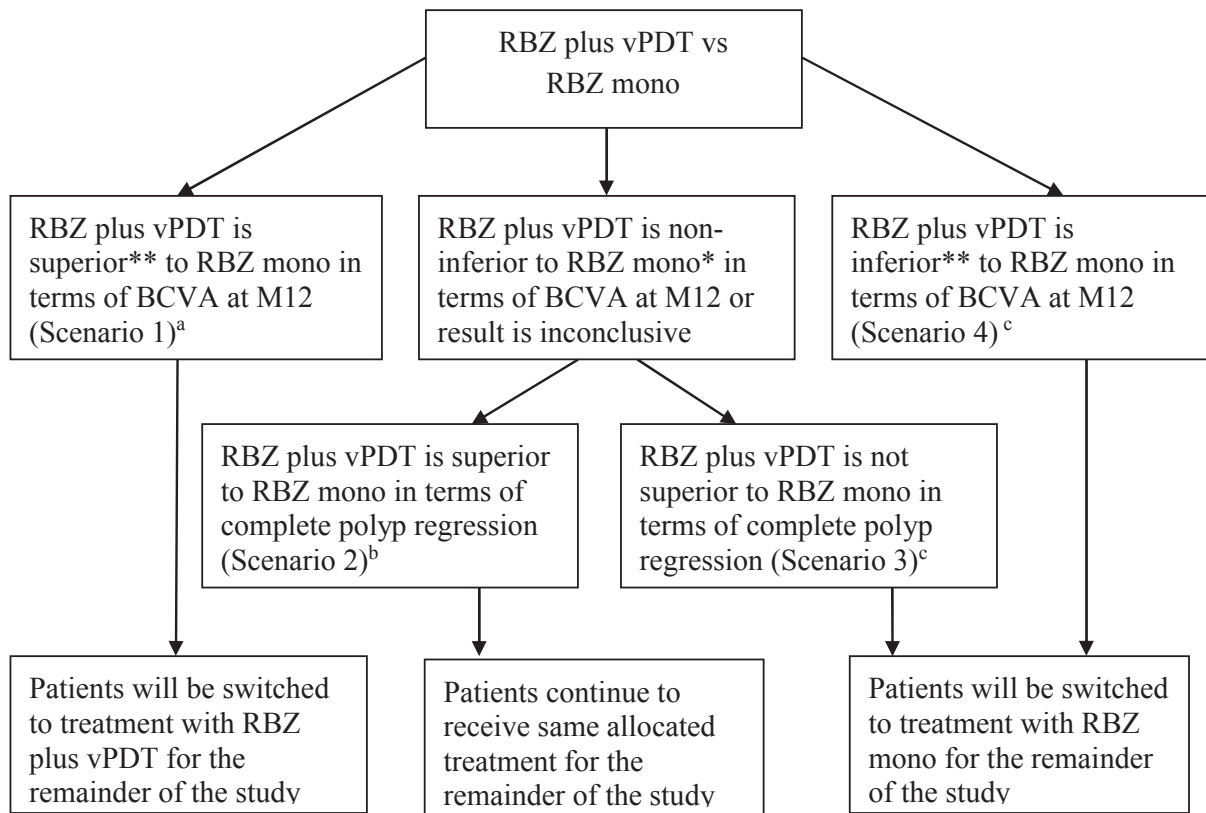
#### **Period: Day 1 to Month 12**

- Arm 1: ranibizumab with verteporfin PDT (label: Ranibizumab 0.5 mg + vPDT)

- Arm 2: ranibizumab monotherapy (label: Ranibizumab 0.5 mg )

Based on the outcome of the primary analysis patients may receive a different treatment for the remainder of the study (see the decision tree). In case of such a treatment switch the treatment labels for the Month 24 analysis will be updated and the output shells in Module 7.1 will be updated. This will be implemented after the Month 12 DB lock, i.e. after the evaluation of the primary analysis.

**Decision tree for continuation after the Month 12 analysis**



RBZ mono: Ranibizumab monotherapy

vPDT: Verteporfin PDT

M12: Month 12

BCVA: Best Corrected Visual Acuity

<sup>a</sup>: Study objectives met, patients will be switched to the more successful treatment (combination therapy)

<sup>b</sup>: Study objectives partially met, study will continue to monitor benefits of polyp regression in Year 2

<sup>c</sup>: Study objectives not met; patients will be switched to the comparator/reference arm (ranibizumab monotherapy)

\*including the cases where the 95% confidence interval of the treatment difference of ranibizumab plus verteporfin PDT versus ranibizumab monotherapy is contained in (-5,0) (ranibizumab plus verteporfin PDT is non-inferior and inferior to ranibizumab monotherapy at the same time) or in (0,5)(ranibizumab monotherapy is inferior and non-inferior to ranibizumab plus verteporfin PDT).

\*\*excluding the cases specified in \*

### **Periods: Day 1 to Month 24 (Day 1- Month 12 / Month 12 - Month 24)**

Following the Month 12 analysis results, patients can be switched to another treatment for the remainder of the study, according to scenarios 1-4 as defined in the decision tree. At the time of switching, some patients who would have been switched might have completed Month 24. These will be evaluated in the treatment group to which they were randomized.

- Scenario 1 (Patients switched to RBZ plus vPDT for the remainder of the study):
  - Arm 1 label: Ranibizumab 0.5 mg + vPDT
  - Arm 2 label: Ranibizumab 0.5 mg
  - Arm 3 label: Ranibizumab 0.5 mg /Ranibizumab 0.5 mg + vPDT
- Scenario 2: treatments remain as randomized, labels are the same as for the Month 12 analyses
- Scenario 3 and 4 (Patients switched to RBZ monotherapy for the remainder of the study):
  - Arm 1 label: Ranibizumab 0.5 mg + vPDT
  - Arm 2 label: Ranibizumab 0.5 mg
  - Arm 3 label: Ranibizumab 0.5 mg + vPDT /Ranibizumab 0.5 mg

## **2.1 General considerations**

Descriptive statistics will include n (number of observations), mean, standard deviation (and standard error when appropriate), median, lower quartile (Q1), upper quartile (Q3), minimum and maximum for continuous variables, and frequencies and percentages for categorical variables.

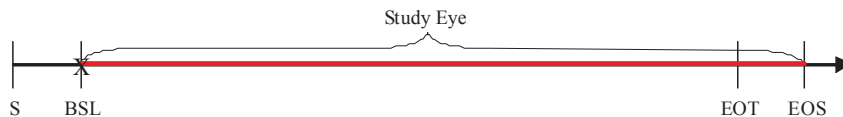
The study eye is the eye identified by the investigator according to the protocol and recorded as such at the screening visit in the CRF.

Study treatment refers to ranibizumab or ranibizumab and verteporfin PDT treatment.

The non-study eye will be defined as the fellow untreated eye if the non-study eye has not been treated with ranibizumab. The non-study eye is the fellow untreated eye until treated with ranibizumab and then becomes the fellow treated eye ([Figure 1 Study Eye, Fellow Untreated Eye and Fellow Treated Eye](#)). (Note: not all non-study eyes will be treated with ranibizumab and a non-study eye may be a fellow untreated eye for the entire study duration.)

### **Figure 1 Study Eye, Fellow Untreated Eye and Fellow Treated Eye**

Study Eye



S=Screening, BSL=Baseline, EOT=End of Treatment, EOS=End of Study, X=First treatment decision for study eye

### Non-study Eye



S=Screening, BSL=Baseline, EOT=End of Treatment, EOS=End of Study, X=First ranibizumab treatment in the non-study eye

The efficacy analyses of this study will be based on the study eye data only. Post baseline will always refer to assessments performed after the start of treatment, i.e. after the first study treatment.

For non-ocular, study eye, and fellow untreated eye summary tables, figures, and listings will be on all patients included in the analysis set population under consideration. Summary tables, figures, and listings for the fellow treated eye will include only those patients in the population under consideration who also received at least one ranibizumab treatment in the non-study eye.

Unless otherwise specified, all confidence intervals (CIs) and *P* values will be two-sided and will be based on the 0.05 significance level.

Assessments documented in the Database as occurring in “both eyes” will be summarized and listed for each eye separately. To facilitate derivations and analysis based on eye (study eye, fellow untreated eye, fellow treated eye) database records for “both eyes” will be split to two records containing identical information as the original record with the exception of the site which shall be recoded to “Right” and “Left”, respectively.

Prior/Concomitant medication, medical history, adverse events will be defined as ocular or non- ocular according to the investigator’s response to ‘site’ on the relevant CRF page.

## 2.2 Analysis sets

The **Screened Set** will consist of all patients who signed the informed consent form (ICF). The data from patients who did not sign an ICF prior to any study procedures will be listed only and not be used in any analyses.

The **Randomized set** will consist of all randomized patients, i.e. of all patient to whom a randomization number has been assigned.

The **Full Analysis Set (FAS)** comprises all patients to whom treatment regimen has been assigned. Following the intent-to-treat principle, patients will be analyzed according to the treatment regimen they are assigned to at randomization. No data will be excluded from the FAS analyses because of protocol deviations.

The **Safety Set** will consist of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment. The statement that a patient had no adverse events also constitutes a safety assessment.

The **Per Protocol Set (PPS)** will consist of all patients in the FAS who followed the treatment regimen as randomized and completed Month 12 without clinically significant protocol deviations.

All efficacy evaluations of Month 12 will be carried out on the FAS. All efficacy evaluation of Month 24 will be carried on FAS. The analysis for the primary efficacy evaluation will be carried out on both the FAS and the PP set. All safety evaluations will be carried out on the Safety set. Within the Safety Set, patients will be analyzed as treated. Please see the following table about analysis sets used for efficacy and safety analyses.

**Table 2-1 Analysis sets and arms used for efficacy and safety analyses by reporting period**

	Period 1: Primary analysis for Month 12		Day 1 to Month 24			
	Efficacy	Safety	Efficacy			Safety
	FAS	SS	FAS			SS
By treatment arm	Arm 1	Arm 1	Scenario 1*	Arm 1	Arm 1	Arm 1
	Arm 2	Arm 2		Arm 2	Arm 2	Arm 2
				Arm 3	Arm 3	Arm 3
			Scenario 2*	Arm 1	Arm 1	Arm 1
				Arm 2	Arm 2	Arm 2
			Scenario 3, 4 *	Arm 1	Arm 1	Arm 1
				Arm 2	Arm 2	Arm 2
				Arm 3	Arm 3	Arm 3

Note: \* please go to page 7 for the definition of arm 1, arm 2 and arm 3.

The study Data Handling Plan, located in CREDI in /Administrative Files (study level)/Validation and Planning documents include protocol deviation population codes and the corresponding actions for excluding or reporting data.



The number and percentage of patients in each analysis set will be summarized based on all randomized patients. The number of patients included in fellow treated eye summaries (i.e. the number of patients who receive at least one treatment in the non-study eye) for the Safety Set will also be presented as not all patients will receive treatment in the non-study eye.

In addition, a listing will be produced to show the patient inclusion/exclusion into each of the analysis sets with the corresponding reason(s) for exclusion. Analysis sets will be summarized for the Month 12/24 analysis.

The analysis will be repeated at Month 24 if the number of fellow treated eyes increases due to patients who received their first treatment in the non-study eye during Treatment Period 2.

If protocol deviations do occur, then the data from specific patients, visits, or evaluations may be excluded from analysis. The criteria and determination of clinically significant protocol deviations will be data based and finalized prior to the Month 12 database lock. After the Month 12 database lock, the set of patients included in the PPS will not be modified, however additional visit specific or assessment specific exclusions may be identified prior to the Month 24 database lock and analysis (e.g., assessment after receipt of a prohibited medication.)

Patients are excluded from analysis sets due to protocol (defined in the DHP (Data Handling Plan)) and non-protocol deviations (based on the definition of the analysis set/according to the SAP).

The protocol deviations are mainly used in excluding entire patients or particular data within a patient from the Per Protocol Set (PPS). However there is one protocol deviation with a severity code of 8 which if recorded excludes that patient from all analysis sets. For deviations which are eye specific, only deviations in the study eye will result in exclusion from the PPS.

To derive the other analysis sets below (FAS, PPS and Safety Set) non-protocol deviations will be used (Table 2-2). No severity codes are defined in the source database for non-protocol deviations. However, for the non-protocol deviations, the relevant severity code (as defined for protocol deviations) with respect to the impact on the analysis sets will be used for programming purposes.

**Table 2-2 Analysis set exclusion summary**

<b>Analysis set (to be excluded from)</b>	<b>Non-protocol Deviations</b>	<b>Assigned Protocol Deviation Severity Codes</b>
Full Analysis Set	Not in the Randomized Set	0
Per Protocol Set	Not in FAS	0
	No baseline BCVA value	1
	No baseline polyp assessment	1
Safety Set	Did not receive at least one study treatment	5
	Did not record at least one post-baseline safety assessment	5

The PPS will consist of all patients in the FAS who complete month 12 without any clinical significant protocol deviations (severity code: 0, 8, 1) as specified in [Table 2-3](#).

**Table 2-3 Protocol deviations and impact on analysis**

Code		Impact on the analysis
8	Exclude from all analyses	Exclude patient completely from all analyses sets.
0	Exclude from all efficacy analyses (including ITT)	Exclude patient completely from the FAS and Per-Protocol Sets.
1	Exclude from Per-Protocol analysis	Exclude patient completely from Per-Protocol Set.
2	Exclude from per-protocol analysis from deviation date onwards	The corresponding deviation date identifies the first visit to be excluded. Data collected on or after the deviation date will not be included in the Per Protocol analyses. The deviation date is defined as the date of the Visit when the PD occurred +1 day
4	Exclude from data analysis on deviation date	Data collected for BCVA on the deviation date will not be included in the randomized set, FAS and Per Protocol analyses
5	Exclude from all safety analyses	Exclude patients completely from Safety set.
49	Report relevant PD in the CSR; include in all analyses	Include in all analysis

Additional exclusions may be added based on final criteria determined prior to DBL.

## 2.3 Assessment windows, baseline and post baseline definitions, missing data handling

### 2.3.1 Baseline and post-baseline definitions

Baseline (day 1) is the date of the first treatment in the study eye.

The baseline value for efficacy and safety variables is the last available, non-missing, value collected prior to first study treatment in the study eye. If a patient is randomized but not treated then the baseline value for a variable is the last available non-missing value collected prior to randomization.

Some baseline assessments may be recorded on the day of the baseline visit. Since the time of the first study treatment in the study eye at this visit is not recorded in the CRF, it is not possible to determine which baseline assessments at the baseline visit were undertaken before and which after the first treatment in the study eye. Hence, only the assessments which, according to the protocol, should have been conducted pre-dose will be assumed to have been done before the first study treatment in the study eye when deriving baseline values recorded on the day of the baseline visit.

All data collected after day 1 are defined as post-baseline.

The study day for a baseline or post-baseline scheduled or unscheduled visit is defined as

$$\text{Study day} = (\text{Date of visit}) - (\text{date of baseline visit}) + 1$$

The study day for a scheduled or unscheduled visit before baseline is defined as

$$\text{Study day} = (\text{Date of visit}) - (\text{date of baseline visit})$$

### 2.3.2 End of treatment / End of study visits / Visit windows

Analyses presented by visit will use the visits/visit numbers as recorded in the database. No visit windows will be defined except for the End of Study and End of Treatment visits (see below) and injections received at unscheduled visits.

Since the End of Study visit is assigned the visit number 777 and the End of Treatment visit is assigned the visit number 776 in the database, the actual visit number will not be available. The following approach will be used to assign an actual visit to the End of Study visit 777 and End of Treatment visit 776. The mapping will only occur once for each patient using the visit date, regardless of any other date collected for each data type (where one exists).

- If a patient has completed the study, the visit = 777 will be assigned the actual visit number 26 (Month 24).
- If a patient has completed treatment, the visit = 776 will be assigned the actual visit number 25 (Month 23).
- If a patient has prematurely discontinued from the study and/or prematurely discontinued treatment, then the visit windows specified in [Table 2-4](#) will be used to assign an actual visit to the visit = 777 and/or visit=776, by comparing the End of Study date to Day 1 for study discontinuation and End of Treatment Period date to Day 1 for treatment discontinuation.

If the End of Study visit and/or the End of Treatment visit are assigned to a visit which already exists, then the assigned visit number will be set to the next one. For example, if a patient discontinues prematurely at Visit 4 (assigned based on the visit windows), but has already a Visit 4, then the End of Study visit will be set to Visit 5.

**Table 2-4 Visit Windows**

Visit number	Visit name	Scheduled visit day	Visit window (study days)	Visit number	Visit name	Scheduled visit day	Visit window (study days)
				14	Month 12	360	345 – 374
2	Baseline / Day 1	1	1	15	Month 13	390	375 – 404
3	Month 1	30	2– 44	16	Month 14	420	405 – 434
4	Month 2	60	45 – 74	17	Month 15	450	435 – 464
5	Month 3	90	75 – 104	18	Month 16	480	465 – 494
6	Month 4	120	105 – 134	19	Month 17	510	495 – 524
7	Month 5	150	135 – 164	20	Month 18	540	525 – 554
8	Month 6	180	165 – 194	21	Month 19	570	555 – 584
9	Month 7	210	195 – 224	22	Month 20	600	585 – 614
10	Month 8	240	225 – 254	23	Month 21	630	615 – 644
11	Month 9	270	255 – 284	24	Month 22	660	645 – 674

Visit number	Visit name	Scheduled visit day	Visit window (study days)	Visit number	Visit name	Scheduled visit day	Visit window (study days)
12	Month 10	300	285 – 314	25	Month 23	690	675 – 704
13	Month 11	330	315 – 344	26	Month 24	720	>= 705

### 2.3.3 Unscheduled visits

All data collected at unscheduled visits will be listed.

Adverse event and exposure to treatment data collected at unscheduled visits will be used.

Efficacy and other data (e.g. patient reported outcomes) collected at unscheduled visits will not be used for any post baseline by visit analyses except when imputing missing efficacy data (see section on handling missing data)

The following data when collected at unscheduled visits will be used for tables and graphs when reporting by scheduled visit.

- Exposure to treatment
- Shift tables and graphs comparing baseline to (worst case) post-baseline
- For vital signs and laboratory data;
  - Summaries of notable abnormalities and shift tables and graphs for the occurrence of values outside the normal range.

Other data collected at unscheduled visits will not be used for tables and graphs analyzing post-baseline data when reporting by scheduled visit.

### 2.3.4 Determination of the Month 12/24 DB cut-off

For Month 24, there is no data cut-off date; all data in the locked database will be included for analysis.

Table 2-5 below defines the cut-off dates for the inclusion of data for the Month 12 analysis. Separate cut-off dates are provided for efficacy, safety (including laboratory data and vital signs) and exposure. Each of these is considered for patients that attend the visit at month 12 and those who do not. Note that “treatment date assigned to the Month 12 visit” is defined as the earliest treatment date in the study eye assigned to the Month 12 visit.

Patient disposition analysis will follow the cut-off points, used for the analyses of efficacy.

**Table 2-5 Cut-off dates for the Month 12 analysis**

Patient classification	Efficacy analyses	Safety (including labs and vital signs) analyses	Exposure analyses
Patient is randomized but not treated	Randomization date	Randomization date	Not applicable
Patient is treated at the month 12 visit	Scheduled visits from day 1 until treatment	Scheduled or unscheduled visits from	Scheduled or unscheduled visits from

Patient classification	Efficacy analyses	Safety (including labs and vital signs) analyses	Exposure analyses
	date assigned to the month 12 visit and BCVA data from unscheduled visits during this period.	day 1 until the day before the treatment date assigned to the month 12 visit and AEs with an onset date equal to the treatment date assigned to the month 12 visit that the investigator has indicated have occurred before treatment on that day (AE occurrence field is marked as "yes" on the CRF) and safety assessments which, according to the protocol, should have been conducted pre-dose on the treatment date assigned to the month 12 visit	day 1 until the day before treatment date assigned to the month 12 visit
Patient attends the month 12 visit but is not administered treatment (ranibizumab, vPDT or sham PDT)	Scheduled visits from day 1 until and including month 12 visit date+7 days And BCVA data from unscheduled visits during this period	Scheduled or unscheduled visits from day 1 until and including month 12 visit date +7 days	Scheduled or unscheduled visits from day 1 until the day before month 12 visit
Patient discontinues study before month 12 visit date	Scheduled visits with planned date between day 1 and first treatment date in the study eye + 374* days included And BCVA data from unscheduled visits during this period	Scheduled with planned date or unscheduled visits between day 1 and first treatment date in the study eye + 374* days included	Scheduled with planned date or unscheduled visits between day 1 and first treatment date in the study eye + 374* days included
Patient who has not discontinued study before month 12 visit date and who does not attend month 12 visit	Scheduled visits with planned date between day 1 and first treatment date in the study eye + 374* days included And	Scheduled with planned date or unscheduled visits between day 1 and first treatment date in the study eye + 374* days included	Scheduled with planned date or unscheduled visits between day 1 and first treatment date in the study eye + 374* days included

Patient classification	Efficacy analyses	Safety (including labs and vital signs) analyses	Exposure analyses
	BCVA data from unscheduled visits during this period		

\* Upper limit of the visit window for mapping early termination visits, see [Table 2-4](#) in the visit windows.

For patients who did not receive a treatment on the Month 12 cut-off date, all events that started on the cut-off date will be included for each respective analysis (e.g., considered before the data cut-off.)

Only treatment related data reported before the cut-off date will be included in the Day 1 to Month 12 exposure analysis. Treatments at Month 12 are part of the Month 24 analysis, e.g., after the data cut-off.

Safety data collected at Month 12, which are recorded after a potential Month 12 treatment with study drug (e.g. post injection intraocular pressure (IOP)), will not be part of the Month 12 analyses periods, but considered as occurring after the Month 12 data cut-offs.

For all other assessments not mentioned above, data for assessment reported before or on the respective cut-off date for the period end will be included for analysis of that period.

### 2.3.5 Safety observation periods

In addition to the selection of data based on the cut-off dates for Month 12, the dates of first treatment in the study eye and non-study eye will be used to define the safety observation period for each anatomical site (non-ocular, study eye, fellow untreated eye, and fellow treated eye) and analysis period. See [Table 2-6 Safety Observation Period](#) for complete definitions of the observation periods.

**Table 2-6 Safety Observation Period**

Assessment	Period Start	Period End
Non-ocular, Study eye, Non-study eye which does not receive treatment up to M12 or M24	date of first treatment in the study eye for periods beginning at Day 1	Date of last visit before data cut-off date for the given analysis period end (Month 12, or Month 24)
Fellow treated eye	date of first treatment in the non-study eye	Date of last visit before data cut-off date for the given analysis (Month 12 or Month 24)

- If the date of first treatment in the non-study eye is after the data cut-off date for Month 12, then no observations will be included in the fellow treated eye safety observation period for the Day 1 to Month 12 analysis periods, respectively. The non-study eye is then to be

counted as not having received any treatment up to Month 12 and as the fellow-treated eye in the Day 1 to Month 24 period.

### **2.3.6 Missing and implausible dates**

The general approach to handling missing dates is shown in [Appendix 16.1.9 Section 3.1](#) and [Section 3.2](#) for dates of AEs, [Section 3.3](#) and [Section 3.4](#) for concomitant medication and [Section 3.5](#) for medical history diagnosis.

The detailed algorithm will appear in PDS document.

### **2.3.7 Missing baseline data**

Missing baseline data will not be imputed. This includes variables which are not allowed to be collected according to local regulations (e.g. race in France).

## **2.4 Patient disposition, background and demographic characteristics**

### **2.4.1 Patient disposition**

Disposition (study completion) at Month 12 and Month 24 will be summarized by tabulating the number and percentage of patients that completed the trial period and also those that discontinued in that trial period, with discontinuations categorized by reason. When considering disposition at Month 12, a patient will be considered to have completed Month 12/Treatment Period 1 if the date of the discontinuation visit is on or after the 12 Month cut-off date as defined in the data selection section. The Month 24/Treatment Period 2 completion will be based directly on the data from the study completion eCRF page, without change. Treatment completion will be summarized in the same manner as patient disposition using data from the treatment completion eCRF page. Disposition and treatment completion will be summarized for patients in the Randomized Set for the Month 12 and Month 24 analyses. Disposition and treatment completion will also be summarized by the visit of termination/completion. Disposition and treatment completion data will also be presented in listings.

The total number of patients screened and the number of patients screened, but not randomized will be summarized, including the reason for screening failure. Demographic data and the reason for non- inclusion into the study will be listed for patients who fail screening. Screening failure summaries will be performed for the Month 12 analysis.

### **Protocol deviation**

All protocol and non-protocol deviations will be summarized through presenting the number and percentage of patients with each deviation.

Please see [Table 2-2](#) for the non-protocol deviations that would result in exclusion from an analysis set and [Table 2-3](#) for major protocol deviations which would result in exclusion from an analysis set. The number of patients with protocol deviations will be presented. The results will be grouped using the broad categories defined in the most recent SOP. Currently these are:

- Patient did not satisfy entry criteria
- Patient received the wrong treatment or incorrect dose
- Patient developed study/treatment withdrawal criteria during the study, but was not withdrawn
- Patient took an excluded concomitant medication
- Others

Patients with multiple protocol deviations will only be counted once at each level of summarization. In addition, a listing of protocol deviations will be produced including the date and study day of the deviation occurrence with the accompanying deviation code and severity. Deviations will be summarized for the Randomized Set for the Month 12 and Month 24 analyses.

#### **2.4.2 Demographic and ocular characteristics**

Descriptive statistics will be provided for patient demographics and baseline ocular characteristics (identification of study and non-study eye (right/left), intraocular pressure (IOP), and central reading center (CRC) Fluorescein Angiography (FA), Color Fundus Photography (CF), Indocyanine Green Angiography (ICGA) and Spectral Domain Optical Coherence Tomography (OCT)) including the baseline values of the primary and secondary efficacy variables (best-corrected visual acuity (BCVA), CRC assessed central subfield thickness (CSFT)) for the Randomized Set for the Month 12 analysis. Eye specific assessments will be summarized. Demographic and baseline ocular characteristics will be listed. Details with respect to the presented variables are given below:

The time from a pre-screening event (e.g. diagnosis of a condition or taking a medication) in days will be derived using the formula;

Time since <event> [days] = date of informed consent – date of event + 1

If it is preferable to display this in years then the above figure should be divided by 365.25.

#### **Demographic variables and vital signs**

##### Continuous variables:

- Age (years), Height (cm), Weight (kg), Body mass index (BMI) (kg/m<sup>2</sup>).
- Vital signs: Sitting pulse (bpm), Sitting diastolic blood pressure (mmHg), and Sitting systolic blood pressure (mmHg).

##### Categorical variables:

- Age group (<50, 50-<65, 65-<75, 75-< 85, ≥85 years)
- Gender (male, female)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Other)



- Ethnicity (Hispanic/Latino, Chinese, Indian (Indian Subcontinent), Japanese, Mixed Ethnicity, Other).

### **Baseline ocular characteristics**

#### Continuous variables:

- Total BCVA score (letters) (study eye, fellow eye)
- Intraocular pressure (mmHg) (study eye)
- FA variable:
  - Total area of leakage (mm<sup>2</sup>) (study eye)
- OCT variable:
  - Central subfield thickness (µm) (study eye)
  - Central subfield volume (µL) (study eye)
  - Central Choroidal Thickness (µm) (study eye)
  - Central 6mm retinal volume (µL) (study eye)
- ICGA variable:
  - Maximum linear dimension of the lesion (GLD, µm) (polyps + Branch vascular network (BVN) ) (study eye)
  - Polyp size (mm<sup>2</sup>) (study eye)
  - Mean time for polyp filling (sec) (study eye)
  - BVN size (mm<sup>2</sup>) (study eye)
  - Mean time for BVN filling (Sec) (study eye)

#### Categorical variables:

- Study Eye (left, right)
- BCVA of Study Eye vs. Fellow Eye (Study Eye is better, Study Eye is worse, the same)
- Total BCVA score (letters) (< 39, 39 <= 54, 54 < 74, >= 74 ) (study eye, fellow eye)
- Intraocular pressure (mmHg) (<22, 22-29, ≥ 30) (study eye)
- High definition/spectral domain OCT type (Cirrus , Spectralis, Topcon, Optovue, Other) (study eye)
- FA variable:
  - Presence of fluorescein leakage (yes, no, can't grade) (study eye)
  - Type of lesion (100% classic, Predominantly classic, Minimally classic, Occult with no classic component, Can't grade) (study eye)
  - CNV location (Subfoveal, Juxtafoveal, Extrafoveal, Margin of the optic disk, can't grade, Not applicable) (study eye)
  - CNV secondary to (Absent, Pathological myopia, AMD, Angioid streaks, Idiopathic, Inflammation, Trauma, can't grade, Not applicable) (study eye)
  - Presence of secondary CNV/CNV not associated with the main PCV lesion (no, yes, can't grade) (study eye)

- OCT variable:
  - Presence of sub-retinal fluid (yes, no, can't grade) (study eye)
  - Cysts visible (yes, no, can't grade ) (study eye)
  - High definition/spectral domain OCT type (Cirrus , Spectralis, Topcon, Optovue, Other) (study eye)
  - Presence of features suggestive of polyps (no, yes, can't grade)
  - Presence of features suggestive BVN (no, yes, can't grade)
- ICGA variable:
  - Presence of polyps (yes, no, can't grade) (study eye)
  - Number of polyps (1,2,3,4,>5) (study eye)
  - Presence of branching vascular network (BVN) (yes, no, can't grade ) (study eye)
  - Presence of Nodular appearance on stereo-pair viewing (yes, no, can't grade) (study eye)
  - Presence of hypo-fluorescent halo around the nodule (yes, no, can't grade) (study eye)
  - Presence of Pulsation of nodule on dynamic ICGA (yes, no, can't grade) (study eye)
  - Evidence of PCV (Absent, Definite, can't grade) (study eye)
- CF variable:
  - Presence of Orange-red subretinal nodules (no, yes, can't grade) (study eye)
  - Presence of Massive submacular hemorrhage (no, yes, can't grade) (study eye)
  - Presence of Sero-sanguinous hemorrhage (no, yes, can't grade) (study eye)
  - Presence of Serous fluid (no, yes, can't grade) (study eye)

### 2.4.3 Relevant medical history

The number and percentage of patients with relevant medical history as recorded in the database (ocular and non-ocular) and current medical conditions will be tabulated by site (non-ocular, study eye, and non-study eye), system organ class (SOC) and preferred term of the MedDRA dictionary. Separate summaries will be presented for histories and current medical conditions (documented in the database as still active at the start of the study). Additionally all information will be listed including the investigator reported term, and the diagnosis/surgery date and day. Analyses will be performed at Month 12/24 and will be based on the Randomized Set.

## 2.5 Study medication

Summaries of study treatment will be presented for the Safety Set for the periods Day 1 to Month 12 using the data cut-off date in the [Section 2.3.4](#) section above and Day 1 to Month 24. The number of patients receiving ranibizumab treatment in the study eye, fellow treated eye or in both eyes will be summarized. Furthermore the number of patients receiving ranibizumab treatment in both eyes on the same day at least once will be summarized.

A patient will be considered to have bilateral treatment with ranibizumab if the patient received ranibizumab injections in both eyes.

The duration of the safety observation period will be summarized descriptively for the study eye and the fellow treated eye. Durations will be calculated as period end date – period start date + 1 for the study eye and fellow treated eye. The period start and stop dates for the safety observation periods are defined in [Table 2-6 Safety Observation Period](#). The number of injections administered per patient for injections in the study eye, injections in the fellow treated eye, and for injections in either eye will be summarized. Both the frequency distribution (number of patients with 1 injection, number of patients with 2 injections, on up to the maximum number of injections for any one patient for the given treatment period) and summary statistics for the number of injections per patient/eye will be presented. The number of treatments with ranibizumab in the study eye received from Month 3 prior to Month 12 / Month 24 will be summarized.

The number of verteporfin / sham PDT treatments administered per patient in the study eye, will be summarized. Both the frequency distribution (number of patients with 1 treatment, number of patients with 2 treatments, on up to the maximum number of treatments for any one patient for the given treatment period) and summary statistics for the number of treatments per patient will be presented.

Injections given at unscheduled visits will be mapped to study visits as per the [Table 2-4](#). The pattern of ranibizumab treatment administrations will be summarized for the study eye. For a given patient, the pattern of ranibizumab treatments will be identified by a series of zero's, one's (and possibly two's) and the letters M and D where a zero indicates the visit occurred and no injection given, and a one (or two) indicates an injection was given, and a M indicates the patient missed the visit and a D indicates the patient discontinued prior to the visit. For example, at the Month 24 analysis, if a patient received injections at baseline, months 1 to 8, 13 and 14, missed months 16 and 18, discontinued prior to month 22 (no injection at month 22), the ranibizumab treatment pattern for that patient would be 111111110000110M0M000DD. In the event that a patient receives two injections within a given visit window, a 2 will be displayed at that visit in the pattern of ranibizumab treatment administration. The number and percentage of patients for each observed dosing pattern will be presented.

At each visit, the number and percentage of patients receiving an injection will be summarized for the study eye. Additionally, the reasons for treatment given or no treatment will be summarized for the study eye by visit. This will include details for disease activity as recorded in the database (i.e. loss of BCVA, OCT abnormality, FA abnormality, ICGA abnormality, clinical abnormality). The denominator at each visit will be the number of patients who for which a treatment decision was recorded in the eCRF for the given eye at that visit.

If a patient receives more than one injection during a given visit window, the patient will be counted only once in the number receiving an injection and only once the denominator; however the reason for dosing for both doses will be tabulated. The number and percentage of patients receiving a PDT application in the study eye at each visit and the reasons for treatment given or not given will be summarized in similar manner as injections.

The ranibizumab dosing administration record will be listed for all patients with a separate listing for the set of patients who received bilateral treatment with ranibizumab. Bilateral treatment means that the patient treated with a in both eyes during the study.

Additionally, a listing of summarized dosing parameters (e.g., total number of injections in the study eye) will be provided. A listing will also be provided detailing data related to the study observation period.

## **2.6 Prior and Concomitant medication**

The number and percentage of patients taking concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary using the Safety Set for the Month 12 and Month 24 analyses. Summaries will be presented over 2 time periods: therapies received prior to the start of study treatment (i.e. medication end date is prior to date first treatment in the study eye) and therapies received after the start of study treatment. For prior medications, separate summaries will be provided for non-ocular, study eye, and non-study eye. For concomitant medications, separate summaries will be provided for non-ocular, study eye, non-study eye.

Treatments that are specified as being taken in both eyes will be included in summaries for both the study eye and the non-study eye. If the site is missing, the data will be queried. If any medication has an incomplete date, this will be handled as described in [Section 2.3.6](#). Concomitant medication records with start date prior to Month 12 cut-off date and end date after Month 12 cut-off date will be listed as “ongoing” instead of listing the actual end date for the Month 12 analysis. Concomitant medication records with blank “end dates” and blank “continuing fields” will also be listed as ongoing at the Month 12 analysis. Prior and prior/concomitant medications will be listed. Concomitant medications will be summarized for the Day 1 to Month 12 and Day 1 to Month 24 analysis periods.

## **2.7 Efficacy evaluation**

All efficacy endpoints analyses for Month 12 and Month 24 described in this section will be performed for the FAS and based on the study eye only. Data from patients who discontinue study treatment will be censored for all efficacy analyses after treatment discontinuation. These data will be listed and used to derive information for efficacy over time after discontinuation of study treatment under alternative treatment or no treatment as applicable. Study and non-study eye data in the database will be listed. Efficacy will be summarized for the period from Day 1 to Month 12 and from Day 1 to Month 24 respectively.

### **2.7.1 Analysis of the primary variables**

The primary objective is to demonstrate that ranibizumab combined with verteporfin PDT is non-inferior to ranibizumab monotherapy in patients with symptomatic macular PCV as assessed by the change in best corrected visual acuity (BCVA) from baseline to Month 12 and superior with respect to complete polyp regression assessed by ICGA at Month 12.

If this is established, the next step will be to demonstrate that ranibizumab combined with verteporfin PDT is superior to ranibizumab monotherapy as assessed by the change in best corrected visual acuity (BCVA) from baseline to Month 12.

### 2.7.1.1 Primary Variables

The primary variables are the BCVA change at Month 12 compared to baseline and the occurrence of complete polyp regression at Month 12 (based on the assessment from the CRC).

Patient will have a complete polyp regression at Month 12 if presence of polyps, as assessed by CRC (recorded in dataset ICG2, variable: PRTPLY1C), has value “No” at Month 12. If presence of polyps is recorded as “Yes” or “can’t grade” at Month 12 then complete polyp regression is not achieved at Month 12.

### 2.7.1.2 Statistical model, hypothesis, and method of analysis

The primary objective of this trial is to show in a first step, that combination treatment (verteporfin PDT + ranibizumab) is non-inferior to ranibizumab monotherapy with respect to the BCVA change from baseline at Month 12 and that combination treatment is superior with respect to occurrence of complete polyp regression at Month 12.

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

Non-inferiority with respect to BCVA:

H01:  $\mu_{\text{combination}} - \mu_{\text{mono}} \leq -\Delta$  versus HA1:  $\mu_{\text{combination}} - \mu_{\text{mono}} > -\Delta$

Superiority with respect to complete polyp regression:

H02:  $p_{\text{combination}} - p_{\text{mono}} \leq 0$  versus HA2:  $p_{\text{combination}} - p_{\text{mono}} > 0$

where  $\mu_{\text{combination}}$  and  $\mu_{\text{mono}}$  are the unknown mean changes from baseline in BCVA at month 12 in the combination therapy and monotherapy and  $p_{\text{combination}}$  and  $p_{\text{mono}}$  are the unknown proportions the combination therapy and monotherapy, respectively.  $\Delta$  is the non-inferiority margin and is pre-defined to be 5 letters. The hypothesis testing with respect to non-inferiority of BCVA will be carried out using an analysis of covariance model including treatment group as factor and (centered) baseline BCVA as continuous variable. The Fisher-test will be performed to test for superiority with respect to complete polyp regression.

Centered baseline means that the overall mean baseline value will be subtracted from the baseline value before being used in the model.

After establishing non-inferiority of BCVA and superiority with respect to complete polyp regression in a second step superiority of BCVA with respect to the BCVA change from baseline to Month 12 will be tested at the one sided level of  $\alpha = 0.025$ .

Superiority with respect to BCVA:

H03:  $\mu_{\text{combination}} - \mu_{\text{mono}} \leq 0$  versus HA3:  $\mu_{\text{combination}} - \mu_{\text{mono}} > 0$

The hypothesis testing with respect to superiority of BCVA will be carried out using an analysis of covariance model including treatment group as factor and (centered) baseline BCVA as continuous variable.

With this testing strategy the overall alpha (family-wise error rate) will be kept at the one-sided  $\alpha$ -level of 0.025 (Maurer et al 1995).

The primary analysis will be conducted within the FAS using the last observation carried forward (LOCF) approach for imputing missing data. Least square means and its standard error will be displayed for each treatment group. The LS means for the difference between the treatment groups' change from baseline, its confidence interval and the adjusted superiority and non-inferiority p-values will be provided.

### 2.7.1.3 Handling of missing values/censoring/discontinuations

Missing values of BCVA and presence of polyp will be handled following the Last Observation Carried Forward (LOCF) method.

### 2.7.2 Supportive analyses

The primary analysis will be repeated for the PPS using the same model as the one used for the primary analysis. Also, the primary analysis for BCVA change from baseline will be done without adjustment for the baseline BCVA and for complete polyp regression using stratified/unstratified Cochran-Mantel-Haenszel Tests. The strata will be derived from the baseline BCVA value (strata 1: baseline BCVA value < 56 letters, strata 2: baseline BCVA  $\geq$  56 letters).

The change from baseline in BCVA at Month 12 will be compared between the two treatments based on the assumption of a "Missing at Random (MAR)" process, i.e. assuming that the statistical behavior of a patient who drops out post-withdrawal is the same as that for a patient remaining in the study and sharing the same covariates and the same measurement history. This sensitivity analysis will be based on a mixed model repeated measurement (MMRM). The MMRM model is fitted to all the scheduled BCVA data collected from Month 1 to Month 12 inclusive. The following fixed effect factors are to be included in the model

- treatment group
- scheduled visit
- 'centered baseline BCVA' and 'lesion type at baseline' (see above)
- treatment group by visit interaction
- visit by centered baseline BCVA interaction

A term for scheduled visit will be included in the repeated statement (in SAS PROC MIXED) and an unstructured correlation matrix will be used thus allowing adjustment for correlations between time points within patients. The Kenward-Roger approximation of degrees of freedom will be used.

Since scheduled visit is in the repeated statement it is important to ensure that each patient has, at most, one observation per scheduled visit.

The comparisons amongst treatment arm will be made using the time by treatment contrasts with ranibizumab used as the control group. For the adjusted treatment by visit contrast (=adjusted mean difference) the mean difference together with its standard error and two-sided confidence interval will be displayed

LS Means and Standard Errors will be displayed for each treatment group, with the adjusted mean difference from baseline, and a 95% Confidence Interval for the difference. P-values as derived via REML will be displayed.

### 2.7.3 Analysis of secondary variables

The analysis of the secondary efficacy objectives will focus on the study eye only and it will be based on the FAS for M12 analysis and for M24 analysis as defined in [Table 2-1](#).

#### 2.7.3.1 Secondary variables

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

1. Change from baseline in BCVA over time up to Month 24.
2. Increase of  $\geq 5$ ,  $\geq 10$ , and  $\geq 15$  letters in BCVA from baseline up to Month 24.
3. Loss of  $< 5$ ,  $< 10$ ,  $< 15$  and  $< 30$  letters in BCVA from baseline up to Month 24.
4. Occurrence of complete polyp regression as assessed by ICGA at Months 3, 6, 12, and 24.
5. Presence of leakage as assessed by FA at Month 3, 6, 12, and 24.
6. Changes in central subfield thickness (CSFT) by SD-OCT from baseline over time.
7. Treatment with ranibizumab and verteporfin PDT
  - Total number of treatments with ranibizumab and verteporfin PDT received in the study eye from baseline up to Month 12 and Month 24
  - The number of treatments with ranibizumab in the study eye received from Month 3 up to Month 12 and up to Month 24
  - Comparison of numbers of ranibizumab injection treatment received by Month 12
8. Hemorrhage
  - Presence of hemorrhage from baseline up to Month 12 and Month 24 (for both serosanguinous hemorrhage and massive submacular hemorrhage)
  - Comparison of hemorrhage presence between treatments at Month 12 and Month 24 (for massive submacular hemorrhage)
- 9a. Flat retina (defined as CSFT  $< 300\mu\text{m}$ , as assessed by investigator)
  - Occurrence of flat retina from baseline up to Month 12 and Month 24 respectively
  - Time to first occurrence of flat retina from baseline till Month 12 and Month 24 respectively
  - Time to first re-occurrence of non-flat retina from patient's first occurrence of flat retina to Month 12 and Month 24 respectively

- 9b. Fluid-free retina (defined as no SFR, nor cyst, nor intraretinal fluid, as assessed by investigator)
- Occurrence of fluid-free retina from baseline up to Month 12 and Month 24 respectively
  - Time to first occurrence of fluid-free retina from baseline till Month 12 and Month 24 respectively
  - Time to first re-occurrence of non-fluid-free retina from patient's first occurrence of fluid-free retina to Month 12 and Month 24 respectively
10. BCVA $\geq$ 69 letters (defined as 20/40 or 69 ETDRS letters)
- Occurrence of BCVA $\geq$ 69 letters for all scheduled visits
  - Time to first occurrence of BCVA $\geq$ 69 letters from baseline up to Month 12
  - Time to first occurrence of BCVA $\geq$ 69 letters from baseline up to Month 24
  - Time to first re-occurrence of BCVA $<$ 69 from patient's first occurrence of BCVA $\geq$ 69 to Month 12
  - Time to first re-occurrence of BCVA $<$ 69 from patient's first occurrence of BCVA $\geq$ 69 to Month 24
11. No disease activity (as reported by evaluating investigator on treatment assessment page)
- Occurrence of no disease activity for all scheduled visits
  - Time to first occurrence of no disease activity from baseline up to Month 12
  - Time to first occurrence of no disease activity from baseline up to Month 24,
  - Time to first re-occurrence of disease activity from patient's first occurrence of no disease activity to Month 12
  - Time to first re-occurrence of disease activity from patient's first occurrence of no disease activity to Month 24

## **Secondary Analyses**

Endpoints for the BCVA change from baseline by visit, and CRC-assessed/investigator-assessed CSFT change from baseline by visit, will be summarized descriptively.

Endpoints for BCVA improvement of  $\geq 5$ ,  $\geq 10$ , and  $\geq 15$ , or BCVA loss  $< 5$ ,  $< 10$ ,  $< 15$ ,  $< 30$ , letters will be summarized by presenting the number and percentage of patients in each treatment achieving the endpoint and the corresponding 95% confidence intervals based on exact methods. A logistic regression model with treatment group as a factor will be conducted with ranibizumab as control group. The estimated odds ratio and the 95% likelihood-ratio confidence interval of the odds ratio as compared to the control group will be presented.

Changes in CRC-assessed CSFT from baseline to Month 12 will be compared between treatment groups using ANCOVA models (with the centered baseline as covariate)/ T-test. The least squared means and standard errors for each treatment arm and treatment differences



along with their 95% confidence intervals will be presented. Two-sided p-values will be presented for each treatment difference.

Figures will be produced showing the BCVA mean change from baseline and CRC-assessed/investigator-assessed CSFT mean change from baseline by treatment over time.

Total number of injections of ranibizumab received in the study eye will be summarized. The number of ranibizumab injections up to Month 12 will be compared between treatment groups by Negative Binomial regression with treatment as factor and exposure time to the study treatment be adjusted. Estimation, 95% confidence interval and two-sided p-value will be provided for the difference between the event rates of treatment injection of two treatment arms.

Presence of hemorrhage (for both serosanguinous hemorrhage and massive submacular hemorrhage) over time will be summarized by treatment arm. Logistic regression model will be used to compare the proportion of hemorrhage (massive submacular hemorrhage) presence between the treatment arms with baseline hemorrhage status and treatment arm as factors. The comparison between treatment arms will be repeated at Month 12 and Month 24 by logistic regression model. The odds ratio, its 95% confidence interval, and two-sided p-value for the treatment comparison will be reported.

Occurrence of flat retina and fluid-free retina will be summarized over time up to Month 12 and Month 24. Kaplan-Meier plot will be provided for time from first treatment in the study eye to the first flat retina (for patients with non-flat retina before first treatment) or time to the first fluid-free retina occurrence (for patients with retinal fluid before first treatment) by treatment arms. If flat retina or fluid-free retina did not occur until the end of the safety observation period, the time to first occurrence of flat retina or time to first occurrence of fluid-free retina will be set to the duration of the safety observation period and will be considered to be censored. Kaplan-Meier curves and summary statistics will be provided for time to the first re-occurrence of a non-flat retina/retinal fluid for patients who previously reached a flat retina/fluid-free retina till Month 12 and Month 24 i.e. the difference between the first time the condition non-flat retina/retinal fluid is fulfilled (for patients who previously reached a flat retina/fluid-free retina) and the time of first occurrence of the condition flat/fluid-free retina, till Month 12 and Month 24. This analysis will be performed on observed data with the following imputation for missing data:

- if between two visits with non-missing data, one or more visits have missing data then we assume that:

Non missing visit 1	Missing visits	Non-missing visit 2
flat retina/fluid-free retina	flat retina/fluid-free retina	flat retina/fluid-free retina
non-flat retina/retinal fluid	non-flat retina/retinal fluid	non-flat retina/retinal fluid
flat retina/fluid-free retina	non-flat retina/retinal fluid	non-flat retina/retinal fluid
non-flat retina/retinal fluid	flat retina/fluid-free retina	flat retina/fluid-free retina

- if no data is collected after a visit, then the patient is censored from that visit onward,

- if no data is collected at screening/baseline, then the patient is excluded from the analysis.

Patients with BCVA $\geq$ 69 and patients with no disease activity will be summarized for all scheduled visits. Kaplan-Meier plot will be provided for time from first treatment in the study eye to the first achieving of BCVA $\geq$ 69 (for patients with BCVA $<$ 69 before first treatment) or time to the first occurrence of no disease activity (for patients with disease activity before first treatment, assuming patients have disease activity prior to Month 3). If BCVA $\geq$ 69 or “no disease activity” was not observed during the study observation period, the time will be set to the duration of the safety observation period and will be considered to be censored. Kaplan-Meier curves and summary statistics will be provided for time to the first re-occurrence of BCVA $<$ 69/disease activity for patients who previously reached and maintained BCVA $\geq$ 69/no disease activity till Month 12 and Month 24 i.e. the difference between the first time the condition BCVA $<$ 69/disease activity is fulfilled (for patients who previously reached and maintained BCVA $\geq$ 69/no disease activity) and the time of first occurrence of the condition BCVA $\geq$ 69/no disease activity, till Month 12 and Month 24. This analysis will be performed on observed data with the following imputation for missing data between two visits with non-missing data: for BCVA, the LOCF method will be used and for disease activity, if between two visits with non-missing data, one or more visits are missing then we assume that:

Non missing visit 1	Missing visits	Non-missing visit 2
No disease activity	No disease activity	No disease activity
Disease activity	Disease activity	Disease activity
No disease activity	Disease activity	Disease activity
Disease activity	No disease activity	No disease activity

- if no data is collected after a visit, then the patient is censored from that visit onward,
- if no data is collected at Month 3, then the patient is excluded from the analysis.

#### 2.7.4 Other efficacy variables/Exploratory analysis

##### Exploratory analyses

To evaluate the correlation between baseline characteristics and changes in BCVA and CSFT, as well as complete polyp regression over time up to Month 24.

- A scatterplot will be provided for polyp size at baseline vs. change in BCVA from baseline to Month 12 / 24. A separate plot will be given for each treatment arm.
- A scatterplot will be provided for polyp size at baseline vs. change in CSFT from baseline to Month 12 / 24. A separate plot will be given for each treatment arm.

- A scatterplot will be provided for time to diagnosis vs. change in BCVA from baseline to Month 12 / 24. A separate plot will be given for each treatment arm.
- A scatterplot will be provided for time to diagnosis vs. change in CSFT from baseline to Month 12 / 24. A separate plot will be given for each treatment arm.
- The BCVA time-course will be summarized for each visit by the baseline status macular hemorrhage

CRC Assessed Fluorescein Angiography (FA), Color Fundus Photography (CP) and Spectral Domain High-Definition Optical Coherence Tomography (OCT):

A shift table will be produced looking at the shift/change from baseline to Month 3, 6, 12 and Month 24 for each of the categorical OCT, FA, CP and ICGA parameters (see baseline ocular characteristics). The number /proportion of patients who develop secondary CNV (diagnosed by FA/ICGA) at Month 3, 6, 12 and Month 24 will be presented.

Summary statistics will be produced for the absolute values and the change from baseline values at each scheduled post-baseline visit for each of the continuous FA, CP, OCT and ICGA parameters (see baseline ocular characteristics). Analysis will be performed at the Month 3, 6, 12 and Month 24 for OCT, FA, CP and ICGA assessed parameters using FAS observed data for the study eye.

A listing will be provided of the CRC assessed FA, CP, OCT and ICGA results. Investigator FA, CP, OCT and ICGA assessments will be presented in a data listing.

To evaluate the flow dynamics of the PCV lesion in ICGA, including time of “dye appearance in BVN and polyps”: BCVA will be summarized by visit, by tertiles of baseline filling time of polyps and by tertiles of baseline BVN size, up to Month 24.

### **2.7.5 Safety evaluation**

All safety analyses will be performed using observed data in the Safety Set using data cut-off dates as described in the [Section 2.3.4](#) and observations as specified for the non-ocular, study eye, fellow untreated eye, and fellow treated eye in [Section 2.3.5](#).

### **Adverse Events**

Adverse events will be deemed treatment emergent if the onset date is on or after start of study treatment /Day 1. All treatment-emergent AEs will be summarized. Any AEs recorded prior to the start of study treatment/Day 1 will be listed together with all other AEs. If any event has an incomplete onset date, this will be handled as described in the [Section 2.3.6](#).

Adverse events will be presented separately by site (non-ocular, study eye, fellow untreated eye, and fellow treated eye) based on the site information as recorded in the database. Adverse events that are reported for both eyes will be summarized and listed for the study eye and the non-study eye (fellow untreated or fellow treated as applicable.) Adverse events will be summarized by presenting the number and percentage of patients having an AE in each primary system organ class and having each individual AE based on the preferred term.

Patients who experienced multiple AEs for a preferred term will be counted once, similarly for patients with multiple AEs per system organ class.

The following AE summaries will be presented for non-ocular events, study eye events, fellow untreated eye events, and fellow treated eye events for the Day 1 to Month 12 and Day 1 to Month 24 analysis periods.

- all adverse events,
- adverse events by maximum severity,
- serious adverse events,
- adverse events leading to study drug discontinuation,
- adverse events suspected to be related to study drug,
- adverse events suspected to be related to ocular injection, and
- adverse events suspected to be related to study drug and/or ocular injection.

In addition for patients who receive ranibizumab treatment in both eyes (any time) or on the same day (at least once), the non-ocular AEs will be summarized.

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

The following AE listings will be provided:

- deaths,
- serious adverse events,
- adverse events leading to study drug discontinuation,
- any AE recorded prior to the start of study treatment/Day 1,
- adverse events related to ocular/systemic safety concerns (as defined in the RMP),
- any AE for patients receiving ranibizumab injections in both eyes

### **Risk Management Plan adverse events**

The number and percentage of patients who report adverse events identified as safety concerns (based on selected preferred terms) by the current version of the Risk Management Plan (RMP) at the time of each database lock (Month 12 and Month 24), will be summarized by risk categories for ocular (study eye and non-study eye) and systemic concerns. Summaries will be presented for Day 1 to Month 12, and Day 1 to Month 24 periods. In addition, the analysis will include number and percentage of patients with each of the preferred terms that define each of the safety concern risk categories. 95% confidence intervals for the percentages of patients in each risk group and for each preferred term within the risk groups will be produced using the exact binominal method for the study eye. In addition, the relative risk

(Ranibizumab 0.5 mg + vPDT/ Ranibizumab 0.5 mg) and 95% CI assuming a normal distribution will be presented.

Detailed specifications to identify which MedDRA preferred terms belong to which risk category will be added to PDS document based on the valid RMP at the time of the database locks.

A listing for AEs of safety concern by preferred term will also be produced.

### **Vital signs**

Vital signs (sitting blood pressure systolic/diastolic and sitting pulse) (absolute and change from baseline values) will be summarized by descriptive statistics, by visit. Shift tables will be presented using the critical values (extended normal ranges with thresholds representing a clinically relevant abnormality, as specified [Table 2-7](#)) to present the number and percentage of patients who have low, normal or high abnormal values at either baseline or post-baseline. Analysis will be based on the patients in the Safety Set for the Day 1 to Month 12 and Day 1 to Month 24 periods.

Patient listings will be provided and values outside these critical value ranges will be flagged.

### **Intraocular pressure (IOP)**

Intraocular pressure absolute values and changes (pre-injection) from Baseline by visit and changes from pre-dose to post-dose assessments within a visit will be descriptively summarized. Additionally, the number and percentage of patients with IOP  $\geq$  30 mmHg will be presented by visit for pre-injection and post-injection assessment as well as for any post-baseline IOP (pre-injection or post-injection), any post baseline pre-injection assessment (not including the assessment prior to first treatment in the study eye), and any post-injection assessment. Summaries will be presented separately for the study eye and for the fellow treated eye for the Day 1 to Month 12 and Day 1 to Month 24 periods.

IOP data will be listed for all patients and IOP values  $\geq$  30 mmHg will be flagged.

### **Other safety assessments**

Child bearing potential and serum and urine pregnancy test results (if applicable) will be listed for female patients.

Ophthalmic examination and post-injection safety assessments (not including IOP) results will be listed.

### **Exploratory analyses**

To explore the safety in patients undergoing bilateral treatment with ranibizumab up to Month 24:

- The number of patients who received bilateral injections of ranibizumab within 7, 14, and 28 days will be summarized

- All the AEs after the first bilateral treatment will be listed with relation to the date of the bilateral treatment (flagged 7, 14 or 28 days after the latest bilateral treatment).

## 2.7.6 Health-related Quality of Life

### Impact of Vision Impairment (IVI)

The Impact of Vision Impairment (IVI) scale will be scored at Day 1, Months 3, 12 and Month 24. The average score at each time-point will be calculated based on the following rules:

- Answers (with score=8) being equal “Don't do this for other reasons” will be excluded from any calculation
- The codes answers to each question/scores (0,1,2,3,4,5) will be reversed in a first step to (5,4,3,2,1,0); in a second step the 6 categories (with the scores ranging from 0-5) will be condensed to the following derived scores (3,2,2,1,1,0)
- Answers to the questions “Paid or voluntary work?”, “Going out to sports events, movies or plays?”, “Favourite pastimes or hobbies?”, “Reading a sign across the street?” will be excluded from further analysis. Only if all answers to the remaining 28 questions are available for a patient, then the data will be used
- Based on the derived scores ranging from 0-3 an average score will be calculated as the average mean of the 28 single scores, i.e the average score lies between 0 and 3.

For analysis purpose, the average raw score will be transformed according to the following formula

$$IVI_{\text{person measure}} = 19.72 * \log(IVI_{\text{raw score}} / (3 - IVI_{\text{raw score}})) + 48.29$$

where log refers to the logarithm with base = 10.

(Lamoureux et al. 2006)

The corresponding transformed absolute person scores (one value for each patient at each time point) and the changes from baseline will be calculated and summarized descriptively at Month 3, 12 and Month 24. In addition for the change in  $IVI_{\text{person measure}}$  from baseline at each time point, an analysis of covariance model including treatment group as factor and the (centered) baseline  $IVI_{\text{person measure}}$  will be conducted, presenting a 95% confidence interval and a 2- sided (exploratory) p-value for the treatment difference. The IVI data will be summarized for the FAS (observed).

NOTE: Only data collected with the Japanese version of the IVI will be considered for the analysis. However the data will be listed including a flag indicating that they were not used for analysis.

The analyses will be repeated with all questionnaires except the questions 20-24 collected with non-Japanese version.

Note: When comparing Chinese version (both traditional and simplified) with the English version, a translation issue was found in the Chinese version scales (questions 20-24), both in simplified and traditional versions.

#### National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25)

Descriptive statistics by treatment group will be provided for the NEI-VFQ-25 composite score and each of the subscale scores (General health, General vision, Ocular pain, Near activities, Distance activities, Social functioning, Mental health, Role difficulties, Dependency, Driving, Color vision, and Peripheral vision) at Day 1, Month 3, Month 12, and Month 24 and for the change from baseline at each time point for those patients with a score at baseline and the relevant post-baseline time point. In addition for the change from baseline of the composite score and each subscore, an analysis of covariance model including treatment group as factor and the corresponding (centered) baseline score will be conducted at Month 12 and 24 (ANCOVA model 1).

The NEI VFQ 25 subscales and composite score change from baseline values will be analyzed at Months 12 and 24 using an analysis of covariance (ANCOVA) model. The ANCOVA models will include terms for treatment, (centered) baseline BCVA and the specific (centered) baseline subscale/composite score as a covariate (ANCOVA model 2). All presented p-values will be two-sided. The NEI VFQ 25 data will be summarized for the FAS (observed).

Each subscore has a range of 0 – 100 (with 100 indicating the best possible response) and will be calculated from the re-scaled raw data. The raw answers will be re-scaled as described below. A missing response will not be re-scaled (except for the response to 15c, see below, which will be re-set to 0 if the response to 15b is 1).

Answers to questions 1, 3, 4 and 15c will be re-scaled as follows:

Answer	Re-scaled value
1	100
2	75
3	50
4	25
5	0

Note that the answer to question 15c will subsequently be adjusted based on the answer to question 15b, as follows: If the answer to 15b is 1 then the answer to 15c will be re-set to 0. If the answer to 15b is 2 or 3 then the answer to 15c will be re-set to missing.

The answer to question 2 will be re-scaled as follows:

Answer	Re-scaled value
1	100
2	80

3	60
4	40
5	20
6	0

Answer to questions 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16 and 16a will be re-scaled as follows:

Answer	Re-scaled value
1	100
2	75
3	50
4	25
5	0
6	.

Answer to questions 17, 18, 19, 20, 21, 22, 23, 24 and 25 will be re-scaled as follows:

Answer	Re-scaled value
1	0
2	25
3	50
4	75
5	100

Subscales will be calculated where one or more of the (re-scaled) responses contributing to that subscale are non-missing, and otherwise set to missing.

- General health subscale = the re-scaled answer to q 1,
- General vision subscale = the re-scaled answer to q 2,
- Ocular pain subscale = the mean of the (non-missing) re-scaled answers to q 4 and 19,
- Near activities subscale = the mean of the (non-missing) re-scaled answers to q 5, 6 and 7,
- Distance activities subscale = the mean of the (non-missing) re-scaled answers to q 8, 9 and 14,
- Social functioning subscale = the mean of the (non-missing) re-scaled answers to q 11 and 13,



- Mental health subscale = the mean of the (non-missing) re-scaled answers to q 3, 21, 22 and 25,
- Role difficulties subscale = the mean of the (non-missing) re-scaled answers to q 17 and 18,
- Dependency subscale = the mean of the (non-missing) re-scaled answers to q 20, 23 and 24,
- Driving subscale = the mean of the (non-missing) re-scaled answers to q 15c, 16 and 16a,
- Color vision subscale = the re-scaled answer to q 12, and
- Peripheral vision subscale = the re-scaled answer to q 10.

The composite score is constructed from the 11 subscales excluding “General health”. The total score will be the average of the non-missing subscales if at least half of the subscales are non-missing, and otherwise set to missing.

In addition, a scatterplot (composite score vs.  $IVI_{\text{person measure}}$ ) will be provided for the baseline values and the changes from baseline to Month 12 and Month 24.

## 2.8 Interim analyses

No interim analyses are planned for this study. However, the primary analysis and key efficacy and safety analyses will be conducted at the end of Treatment Period 1, at the Month 12 database lock; i.e., at the time point when all patients still in the study have completed the Month 12 visit. The outputs produced at the Month 12 database lock are given in TFL shells – Month 12.

The analysis of the complete study data, including data from both treatment periods and the Post-dose Follow-up Period will be performed when all patients have either completed the post-dose follow-up or have discontinued the study.

## 2.9 Sample size calculation

The sample size calculation for the primary analyses is based on the FAS (LOCF) and the following assumptions:

- Proportion of patients with complete polyp regression at Month 12: combination therapy arm: 0.5, ranibizumab monotherapy: 0.2. The assumption is based on clinical feedback. Similar differences of proportions (with higher absolute values) were observed in EVEREST: During the 6-month study EVEREST (Koh et al 2012) the least favorable difference was observed as 0.72 (combination therapy) and 0.33 (ranibizumab monotherapy).
- Change in BCVA from baseline to Month 12:
  - The standard deviation (SD) is 14 letters. Justification: This SD was observed in the study Sustain (patients with wet AMD) (Holz et al 2011). The SD for the BCVA change from baseline to Month 6 in Sustain was comparable to the SD observed in the 6-month study EVEREST (with PCV patients), i.e. this SD is considered as the closest estimate.

- Treatment difference ( $=\Delta$ ) between combination therapy and ranibizumab monotherapy with respect to the BCVA change from baseline to Month 12. Rather than providing a single assumption for the treatment difference, the sample size /power calculation will be provided for  $\Delta$  equal 0, 1, 2, 3, 4, 5 letters where (e.g.) a  $\Delta = 4$  stands for: The mean change from baseline at Month 12 is 4 letters higher in the combination therapy group compared to ranibizumab monotherapy. Justification: Within the VEREST study there exist 2 estimates for the  $\Delta$ : Estimate 1: (Descriptive) Difference of the mean change from baseline at Month 6: 1.7 letters. Estimate 2: Difference based on a model including the baseline BCVA value (i.e. adjusting the treatment effect for baseline BCVA imbalance): 4 letters.
- Data of all patients will be used for the primary analysis through the use of imputation of missing data.

Based on the assumptions above the “marginal” power / sample size for each primary outcome measure is:

- Superiority of the combination therapy vs. ranibizumab monotherapy with respect to the proportion of patients achieving complete polyp regression at Month 12:
  - One sided  $\alpha = 0.0125$ , exact Fisher test: n = 160 patients per arm lead to a power > 0.99

Non-inferiority of the combination therapy vs. ranibizumab monotherapy with respect to the mean BCVA change from baseline at Month 12: Power / sample size scenarios based on n = 160 patients per arm and a non-inferiority margin of 5 letters.

	$\Delta = 5$ letters	$\Delta = 4$ letters	$\Delta = 3$ letters	$\Delta = 2$ letters	$\Delta = 1$ letter	$\Delta = 0$ letters
$\alpha = 0.025$	>0.99	>0.99	>0.99	>0.99	0.96	0.88

(Student’s 2 sample t-test was used assuming equal variances.)

Superiority of the combination therapy vs. ranibizumab monotherapy with respect to the mean BCVA change from baseline at Month 12: Power / sample size scenarios based on n = 160 patients per arm.

	$\Delta = 5$ letters	$\Delta = 4$ letters	$\Delta = 3$ letters	$\Delta = 2$ letters	$\Delta = 1$ letter	$\Delta = 0$ letters
$\alpha = 0.025$	0.88	0.72	0.48	0.24	0.09	0.025

(Student’s 2 sample t-test was used assuming equal variances.)

Reason for Student’s 2 sample t-test: Based on the EVEREST data it is expected that the baseline BCVA value will impact the change in BCVA (e.g.) due to ceiling effects. However each arm in the study EVEREST had only 20 patients which does not allow for a precise estimation of subgroup effects (mean and SD), with subgroups based on baseline BCVA or adding baseline BCVA as a regression effect without further assumptions. Therefore the power is based on the 2 sample situation, while acknowledging that incorporating baseline BCVA information into the statistical model may lead to an increase of power.

The “combined” power (= P (H1 and H2,  $\alpha$ )) to achieve non-inferior BCVA and superiority with respect to complete polyp regression at the one-sided level of  $\alpha = 0.025$  is at least

	$\Delta = 5$ letters	$\Delta = 4$ letters	$\Delta = 3$ letters	$\Delta = 2$ letters	$\Delta = 1$ letter	$\Delta = 0$ letters
Power	0.98	0.98	0.98	0.98	0.95	0.87

The calculation is based on the following formula:

- Claim non-inferior BCVA with a p-value below  $\alpha = 0.025$  and superiority with respect to polyp regression with a p-value below  $\alpha = 0.025$ .
- $1 \geq P(H1, \alpha \text{ or } H2, \alpha) = P(H1, \alpha) + P(H2, \alpha) - P(H1, \alpha \text{ and } H2, \alpha)$  and  $P(H1, \alpha \text{ and } H2, \alpha) \geq P(H1, \alpha) + P(H2, \alpha) - 1$ , where e.g.  $P(H1, \alpha)$  denotes the “marginal” power for non-inferior BCVA from above (at the level of  $\alpha$ ).
- Please note, that in case the “marginal” power was  $\geq 0.99$ , the value 0.99 was used for the calculations and that the table includes the lower boundary of the inequality.

The “combined” power (= P (H1 and H2 and H3,  $\alpha$ )) to achieve non-inferior BCVA, superiority with respect to complete polyp regression and superior BCVA at the one-sided level of  $\alpha = 0.025$  is at least

	$\Delta = 5$ letters	$\Delta = 4$ letters	$\Delta = 3$ letters	$\Delta = 2$ letters	$\Delta = 1$ letter	$\Delta = 0$ letters
Power, n=160	0.87	0.71	0.47	0.23	0.08	0.015

The calculation is based on the following formula:

$$P(H3, \alpha \text{ and } H2, \alpha) \geq P(H3, \alpha) + P(H2, \alpha) - 1$$

as non-inferiority is implied by superiority of BCVA.

The sample size calculations were performed using nQuery Advisor 7.0.

## 2.10 Change to protocol specified analyses

The following two variables were removed from the list of secondary variables from the planned analyses as described in detail in the protocol:

- Maintenance of BCVA (within 5 letter change) at Month 12 and 24 compared to the BCVA at the time point of first ranibizumab treatment interruption.
- Change in BCVA at Month 12 and 24 compared to the time point of first ranibizumab treatment interruption.

These variables were introduced to assess if patients treated with ranibizumab as PRN are able to maintain visual acuity during the maintenance phase. The decision has been made to remove these analyses for the following reasons:

- we will present change in BCVA from baseline over time by visit. This can be used to assess maintenance of BCVA (within 5 letter change) at Month 12 and 24 compared to the BCVA at Month 3.
- Treatment initiation with monthly dosing of ranibizumab followed by the as-needed treatment regimen in this study is consistent with the product label from most participating countries. The as-needed treatment regimen of ranibizumab with monthly monitoring of VA and/or OCT is supported by a wealth of scientific evidence (The PrONTO trial (Lalwani et al 2009), the CATT trial (Martin et al 2011, Martin et al 2012)). Moreover, the analyses for first time to “no disease activity” and relapse (see Section 2.7.3) are addressing a more pertinent clinical question for the patient and physician, in terms of disease management. Actually, they are similar to those performed in SUSTAIN (CRFB002A2303), in patients with subfoveal choroidal neovascularization (CNV) related to age-related macular degeneration (AMD) for the following variables:
  - The time to first re-treatment (after Month 2),
  - Proportion of patients without need for re-treatment after Month 2

In EVEREST I (CBPD952A2209), in PCV patients, time to first re-treatment and number of retreatments have been analyzed.

## 2.11 SAS code for analysis

### SAS code for Clopper-Pearson Exact Binominal CI

The 95% binomial (Clopper - Pearson) CI will be assessed for the number of patients with a complete polyp regression, the incidences of RMP safety concerns, the number of patients with BCVA improvement of,  $\geq 5$ ,  $\geq 10$ , and  $\geq 15$  letters, and number of patients with loss of BCVA from baseline 5,  $< 10$ ,  $< 15$ ,  $< 30$  letters. The Clopper - Pearson CI will be performed using the SAS procedure PROC FREQ with the BINOMIAL option, 95% CI values are reported under "Exact Conf Limits" from the resulting SAS<sup>®</sup> Output. The following SAS<sup>®</sup> code will be applied:

SAS code for Clopper - Pearson's confidence interval:

```
PROC SORT DATA=<input dataset>;
      BY treatmentvar;

RUN;

PROC FREQ DATA=<input dataset>;
      BY <byvar>;
      TABLES RESP / BINOMIAL (EXACT LEVEL='1') alpha=0.05;
      ods output oneWayFreqs= Bin_freq;
      ods output binomialCLs= Bin_CL;

RUN;
```

where

RESP indicates if event (for e.g. AE, BCVA improvement) occurred or not (1=Yes, 0=No)

<byvar> is list of required by variables for analysis (e.g., risk category/preferred term for AEs, BCVA category for BCVA improvement letters.)

Note

- The data must be sorted by treatment in order to use the BY command which obtains results for each treatment arm.
- The TABLES command specifies the binary variable(s) of interest
- The BINOMIAL option with EXACT specifies that a Clopper-Pearson exact confidence interval is produced
- The LEVEL = '1' specifies that the proportions displayed corresponds to the proportions of 1s. Note that 1 must be within single quotes.
- ALPHA = 0.05 specifies that the 95% confidence limits are produced
  - If the number of events is zero or is equal to the number of observations then the approach above produces a one-sided 97.5% confidence interval. To ensure that a

95% confidence interval is produced in such cases, the value of alpha should be changed to 0.10.

- The ODS OUTPUT options save the information used in the displays for later use.

---

### SAS code for Cochran-Mantel-Haenszel (CMH) test

The two-sided CMH test will be performed using SAS procedure PROC FREQ with the CMH option in the TABLES statement. Categorized visual acuity in the study eye at baseline will be the stratification variables. The variables <treatment> and <response> determine the rows and columns of the tables.

```
PROC FREQ data = <input_dataset sorted> noprint;
  TABLES <stratavar1> * <treatmentvar> * <responsevar> / CMH
          Expected out=results outexpect;
  OUTPUT OUT = <output_dataset> (keep =P_CMHRMS) CMH;
RUN;

DATA signcheck;
  set results;
  where <responsevar> =1 and <treatmentvar> =" Ranibizumab 0.5 mg
+ vPDT";
  diff=count-expected;
RUN;

PROC MEANS data=signcheck sum;
  var diff;
RUN;
```

As we want to test superiority, the one-sided p-value can be computed using:

- If the difference between the number of events in patients treated with Ranibizumab 0.5 mg + vPDT and the expected number of events under the null hypothesis that the event probability is the same for Ranibizumab 0.5 mg + vPDT and Ranibizumab 0.5 mg is positive then one-sided p-value = (0.5\*two-sided p-value)
  - Otherwise then one-sided p-value = 1-(0.5\*two-sided p-value)
-

### SAS code for Fisher's exact test

The statistical testing of difference in the number of patients with a complete polyp regression will be tested using a Fisher's exact test. It will be performed using SAS procedure PROC FREQ with the FISHER option in the TABLES statement.

```
PROC FREQ data = <input_dataset sorted> noprint;
  BY <visit>;
  TABLES <responsevar>*<treatmentvar> / exact binomial;
ods output fishersexact=fisher_test;
```

**RUN;**

As we want to test superiority, the one-sided p-value can be computed using:

If the dataset is ordered such that Ranibizumab 0.5 mg + vPDT is the first column in frequency table and complete polyp regression = "yes" the first row then the one-sided p-value for superiority is the right-sided p-value XPR\_FISH. Indeed, the right-tail probability is the probability of all tables such that the (1,1) cell value (upper left corner) is greater than or equal to the one observed under the condition that the row and column marginal totals are held fixed.

=====

### SAS code for ANCOVA analysis

The ANCOVA analysis will be performed using SAS procedure PROC MIXED.

```
PROC MIXED data = <input_dataset sorted>;
  BY <visit>;
  CLASS <stratavar1> <stratavar2> <treatmentvar>;
  MODEL <responsevar> = <stratavar1> <stratavar2>
<treatmentvar> <Baselinevar>;
  LSMEANS <treatmentvar> /PDIFF=all CL alpha=0.05 OM;
OM; RUN;
```

To get one-sided p-value for non-inferiority test (margin = 5): add -5 letters to control group (Ranibizumab 0.5 mg) and re-run the above code with alpha=0.025 and PDIFF=controlu('Ranibizumab 0.5 mg ').

To get one-sided value for superiority test: re-run the above code with alpha=0.025 and PDIFF=controlu('Ranibizumab 0.5 mg ').

Note: The baseline value should be centered (the overall mean baseline value will be subtracted from the baseline value before being used in the model).

=====

### SAS code for MMRM analysis

Since scheduled visit is in the repeated statement it is important to ensure that each patient has, at most, one observation per scheduled visit. This should be checked using PROC SORT and NODUPKEY.

To avoid potential problems with a bug in SAS reporting an infinite likelihood, the data will be sorted by patient and visit before using PROC MIXED.

For the appropriate treatment difference, we need to sort or code the treatments appropriately before using this model.

The comparison of interest is found by using the SAS code below. Note that for this illustrative example:

- the data are stored in the file data\_set
- the codes for the treatment arms (treatmentvar)
- y = change from baseline BCVA for all scheduled visit up to at Month 12
- stratum = lesion type at baseline
- bsl = centered baseline BCVA
- the data from post-baseline visits up to month 12 are included in the analysis
- ALPHA = 0.05 produces two-sided 95% confidence intervals

```
PROC SORT DATA = data_set nodupkey;
    BY patient visit;
RUN;
PROC MIXED DATA = <<data_set>> METHOD=REML;
    CLASS <treatmentvar> (REF = "Ranibizumab 0.5 mg ") stratum visit
patient;
    MODEL y = <treatmentvar> visit <treatmentvar>*visit stratum bsl
visit*bsl
    / SOLUTION OUTP = pred DDFM = KR;
    REPEATED visit /SUBJECT = patient TYPE = <un> r rcorr GROUP =
<treatmentvar>;
    LSMEANS <treatmentvar>*visit /PDIFF = all CL ALPHA = 0.05 SLICE
= visit OM;
    ods output LSMeans=LSMEAN;
    ods output Diffs=Diff_LSM (WHERE=(VISIT=_VISIT));
RUN;
```



To get one-sided p-value for non-inferiority test (margin = 5): add -5 letters to control group (Ranibizumab 0.5 mg) and re-run the above code with alpha=0.025 and PDIFF=controlu('Ranibizumab 0.5 mg ' 'Month 12').

To get one-sided value for superiority test: re-run the above code with alpha=0.025 and PDIFF=controlu('Ranibizumab 0.5 mg ' 'Month 12').

Note: The baseline value bsl should be centered (the overall mean baseline value will be subtracted from the baseline value before being used in the model).

If the model with the unstructured correlation matrix fails to converge then modifications shall be made in the following order.

- Remove the GROUP = trtc option
- Re-instate the GROUP = trtc option and replace un by VC
- Re-instate the GROUP = trtc option and replace un by CS
- Re-instate the GROUP = trtc option and replace un by AR(1)
- Re-instate the GROUP = trtc option and replace un by TOEP
- Remove the GROUP = trtc option and replace un by VC
- Remove the GROUP = trtc option and replace un by CS
- Remove the GROUP = trtc option and replace un by AR(1)
- Remove the GROUP = trtc option and replace un by TOEP

Removing the GROUP = trtc option assumes that the correlation matrix is equal across the treatment arms. The other modifications replace the unstructured correlation matrix by those with the following assumptions (in the same order) variance components, compound symmetry, first order autoregressive and Toeplitz.

=====

#### **SAS Code for Negative Binomial Analysis:**

The Negative Binomial analysis will be performed using SAS procedure PROC GENMOD.

The comparison of interest is found by using the SAS code below. Note that for this illustrative example:

- the data are stored in the file data\_set
- the codes for the treatment arms (treatmentvar)
- y = total number of injections up to Month 12
- lrisk=log(study observation period)

```
PROC GENMOD DATA = <<data_set>>;
  CLASS <treatmentvar>;
  MODEL y = <treatmentvar> / DIST =NEGBIN link=log offset=lrisk
lrci type3 wald;
  lsmeans <treatmentvar> / cl diff exp;
RUN;
```

=====

### SAS Code for Logistic regression:

#### For the analysis related with the BCVA improvement and BCVA loss:

If the proportion of events is expected to be very low (e.g. fewer than five) or very high then an exact logistic regression approach should be considered. The SAS code for performing exact logistic regression for the example above is given below.

```
PROC LOGISTIC DATA= <<data_set>>;
  BY <<Strata>>;
  CLASS <treatmentvar> (REF = "Ranibizumab 0.5 mg ") / PARAM=REF;
  MODEL <<Dependent variable>> (EVENT = '1') = <treatmentvar>
/ALPHA = 0.05;
  EXACT <treatmentvar>;
  ODS OUTPUT ExactParmEst = exact_parameter_estimates;
  ODS OUTPUT ExactOddsRatio = exact_odds_ratios;
RUN;
```

Where,

1. Dependent variable = status for the each stratum at month 12 or month 24
2. Treatmentvar = Treatment variable
3. Strata = BCVA improvement of,  $\geq 5$ ,  $\geq 10$ , and  $\geq 15$  letters, or BCVA loss  $< 5$ ,  $< 10$ ,  $< 15$ ,  $< 30$  as per defined in above section.

Note

- The reference levels are specified in the CLASS statement.
- The option PARAM = REF ensures that the other levels of the class variables are compared to its reference level.
- The option EVENT = '1' in the model statement specifies that the proportion of observations coded as 1 are analyzed.
- The variables specified in the model statement are those included in the logistic regression model.
- The ODS OUTPUT ExactParmEst specifies the file used to store the two-sided p-values.

- The ODS OUTPUT ExactOddsRatio specifies the file used to store the odds ratios and their two-sided confidence intervals.

**For the analysis of presence of Hemorrhage:**

```
PROC LOGISTIC DATA= <<Data_set>>;
  CLASS <treatmentvar> (REF="Ranibizumab 0.5 mg ")/PARAM=REF;
  MODEL <<Dependent variable>> (EVENT = '1') = <treatmentvar>
baseline;
  ODS OUTPUT PARAMETERESTIMATES=parameters;
  ODS OUTPUT ODDSRATIOS= OR;
RUN;
```

Where,

1. Dependent variable = hemorrhage status at month 12 or month 24
2. Treatmentvar = Treatment variable
3. Baseline = Baseline hemorrhage status

Note

- The reference levels are specified in the CLASS statement.
- The option PARAM = REF ensures that the other levels of the class variables are compared to its reference level.
- The option EVENT = ‘1’ in the model statement specifies that the proportion of observations coded as 1 are analyzed.
- The variables specified in the model statement are those included in the logistic regression model.
- The ODS OUTPUT PARAMETERESTIMATES specifies the file used to store the two-sided p-values. The ODS OUTPUT ODDSRATIOS specifies the file used to store the odds ratios and their two-sided confidence intervals.
- Use the exact statement “EXACT <treatmentvar>;” if the computation time is reasonable.

---

---

**SAS Codes for Kaplan-Meier Plot**

The time to event analysis will be performed using SAS procedure PROC LIFETEST.

```
ODS GRAPHICS ON;
PROC LIFETEST DATA=<<data_set>> PLOTS=survival (failure
test atrisk(outside(0.15))=0 to 360 by 30);
  TIME T * Status (0);
  STRATA <treatmentvar>;
RUN;
```

where:

- T is the survival time.
- the variable Status indicates censoring and 0 indicates a censored time.

The option OUTSIDE(0.15) reserves 15% of the vertical graph window for the at-risk table. It can be adjusted.

Plots will be created separately for month 12 and 24 analysis. Accordingly, atrisk option number will be change.

### SAS Codes for Kaplan-Meier Table

The summary statistics for time to event analysis will be performed using SAS procedure PROC LIFETEST.

```
PROC LIFETEST DATA=<<data_set>>;
  TIME T * Status (0);
  STRATA <treatmentvar>;
  ODS OUTPUT CensoredSummary=censorsum
             Means=mean
             Quartiles=quartiles;
RUN;
```

where:

- T is the survival time.
- the variable Status indicates censoring and 0 indicates a censored time.

## 2.12 Notable ranges for vital signs

The criteria for clinically notable abnormal vital signs are shown below in [Table 2-7](#). In order to be identified as being potentially clinically notable abnormal, an on-treatment vital signs value would need to meet the criterion value, and represent a change of at least the magnitude noted in the change column.

**Table 2-7 Clinically Notable abnormal vital signs**

<b>Variable</b>	<b>Criteria</b>	<b>Change relative to Baseline</b>
Pulse rate	≥120 bpm ≤50 bpm	increase of ≥15 bpm decrease of ≥15 bpm
Systolic blood pressure	≥180 mm Hg ≤90 mm Hg	increase of ≥20 mm Hg decrease of ≥20 mm Hg
Diastolic blood pressure	≥105 mm Hg ≤50 mm Hg	increase of ≥15 mm Hg decrease of ≥15 mm Hg

### 3 Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

#### 3.1 Adverse Event End Date Imputation

For the purpose of date imputation the treatment follow up period date is defined as the last available visit date, i.e. including unscheduled visits after the end of study visit.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

#### 3.2 Adverse event start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	( 1 ) No convention	( 1 ) No convention	( 1 ) No convention	( 1 ) No convention
YYYY < TRTY	( 2.a ) Before Treatment Start	( 2.b ) Before Treatment Start	( 2.b ) Before Treatment Start	( 2.b ) Before Treatment Start
YYYY = TRTY	( 4.a ) Uncertain	( 4.b ) Before Treatment Start	( 4.c ) Uncertain	( 4.c ) After Treatment Start
YYYY > TRTY	( 3.a ) After Treatment Start	( 3.b ) After Treatment Start	( 3.b ) After Treatment Start	( 3.b ) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).

2. Else AE start reference date = treatment start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
  - a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
  - b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
  - a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
  - b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
  - a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
  - b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
  - c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

### **3.3 Concomitant medication end date imputation**

1. If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.
2. Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).

- If the CM end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).

If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date.

### 3.4 Concomitant medication start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	( 1 ) Uncertain	( 1 ) Uncertain	( 1 ) Uncertain	( 1 ) Uncertain
YYYY < TRTY	( 2.a ) Before Treatment Start	( 2.b ) Before Treatment Start	( 2.b ) Before Treatment Start	( 2.b ) Before Treatment Start
YYYY = TRTY	( 4.a ) Uncertain	( 4.b ) Before Treatment Start	( 4.a ) Uncertain	( 4.c ) After Treatment Start
YYYY > TRTY	( 3.a ) After Treatment Start	( 3.b ) After Treatment Start	( 3.b ) After Treatment Start	( 3.b ) After Treatment Start

- If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
- If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
  - If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
  - Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
- If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
  - If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
  - Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
- If the CM start date year value is equal to the treatment start date year value:



- a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior to treatment start date.
- b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
- c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

### **3.5 Medical history date of diagnosis imputation**

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If DIAG year < treatment start date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
  - else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)
- If DIAG year = treatment start date year
  - and (DIAG month is missing OR DIAG month is equal to treatment start month), the imputed DIAG date is set to one day before treatment start date
  - else if DIAG month < treatment start month, the imputed DIAG date is set to the mid-month point (15MON YYYY)
  - else if DIAG month > treatment start month → data error
- If DIAG year > treatment start date year → data error

## References

- Busbee, Brandon G., et al (2006). Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology* 120(5): 1046-1056.
- Koh, Adrian, et al. (2012). EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina* 32(8): 1453-1464.
- Lalwani GA, Rosenfeld PJ, Fung AE, et al (2009) A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol*; 148(1):43-58
- Lamoureux, Ecosse L., et al. (2006). The Impact of Vision Impairment Questionnaire: an evaluation of its measurement properties using Rasch analysis. *Investigative ophthalmology and visual science*, 47(11), 4732.
- Holz, Frank G., et al. (2011). Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. *Ophthalmology*; 118(4):663-71.
- Martin DF, Maguire MG, Fine SL, et al (2012) Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: Two-year results. *Ophthalmology*; 119:1388-98.
- Martin DF, Maguire MG, Ying GS, et al (2011) Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*; 364:1897-908.
- Maurer W, Hothorn LA, Lehmacher W (1995). Multiple comparisons in drug clinical trials and preclinical assays (a-priori ordered hypotheses). In: Vollmar J (ed). *Testing Principles in Clinical and Preclinical Trials. Biometrie in der chemisch-pharmazeutischen Industrie* 6. Stuttgart/New York: Gustav Fischer; p. 3–18