Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ranibizumab (rbe)

Proprietary Product Name: Lucentis

Sponsor: Novartis Pharmaceutical Australia Pty Ltd

14 August 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

1. List of commonly used abbreviations

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine aminotransferase
ALP	Alkaline Phosphatase
AMD	Age-related Macular Degeneration
AST	Aspartate aminotransferase
BCVA	Best-corrected visual acuity
BRVO	Branch Retinal Vein Occlusion
CER	Clinical Evaluation Report
CF	Color fundus
CFT	Central Foveal Thickness
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency)
CNV	Choroidal Neovascularization
CRT	Central Retinal Thickness
CRVO	Central Retinal Vein Occlusion
CSR	Clinical Study Report
D	Dioptre
DME	Diabetic Macular Edema e
eCRF	electronic Case Report/Record Form
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography/Angiogram
FDA	Food and Drug Administration
IOP	Intraocular Pressure
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Meaning
OCT	Optical Coherence Tomography
PDT	Photodynamic therapy
PM	Pathologic Myopia
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RPE	Retinal pigment epithelium
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SCS	Summary of Clinical Safety
SOC	System Organ Class
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VEGFR-1	Vascular Endothelial Growth Factor Receptor 1
VEGFR-2	Vascular Endothelial Growth Factor Receptor 2
vPDT	Visudyne (verteporfin) Photodynamic Therapy

2. Clinical rationale

The following information has been taken from the sponsor's covering letter verbatim:

'*Pathological myopia causes severe loss of vision and is one of the major causes of legal blindness due to retinal disease in a younger, working age population.*

PM results from an abnormal stretching of the eyeball (axial length > 26 mm + myopia < -6 diopters) causing severe anatomical changes at the posterior pole. As a result breaks of the retinal pigment epithelium (RPE)/Bruch's membrane (lacquer cracks) will induce the formation of hypoxic and atrophic area adjacent to RPE and will trigger the process of Vascular endothelial growth factor (VEGF, signal protein) release and abnormal new vessels formation, causing damage of RPE and visual impairment by blood and fluid accumulation.

The current standard of care for CNV secondary to PM is Novartis' Visudyne PDT; it has demonstrated its ability to maintain but not improve visual acuity (letters) from baseline over 1 or 2 years of treatment. Therefore, an unmet need remains, and the use of off-label anti-VEGF, for example Lucentis, in PM has become the first line treatment choice in clinical practice in the last years.'

Comment: The sponsor's clinical rationale is acceptable. Pathologic myopia is more common in Asian populations (9-21%) compared with Caucasian populations (2-4%).[1] Macular CNV is the

most common vision threatening complication of PM, and it has been estimated that in patients with PM the risk of developing CNV is 5-11%.[1] In patients with myopic CNV the risk of developing the condition in the fellow eye is estimated to be 30% within 8 years.[1] The disease occurs more commonly in females compared with males (estimated 67% versus 33%, respectively).[1] More than 50% of CNV affected PM patients have a presenting age of 50 years or less,[1] and the condition has a poor prognosis with a significant risk of visual deterioration.[2]

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission was presented in Common Technical Document (CTD) format. Both hard and electronic copies of the submission were presented. The clinical evaluator worked from hard copies of Module 1 and Module 2 and a copy of the full submission on the CD. The CD was comprehensive, well-structured and easy to navigate. The CD hyperlinks worked without problem using an Adobe PDF reader. The submission included the following clinical information:

- Module 5
  - one pivotal, Phase III clinical efficacy and safety study (RFB002F2301).
  - one Phase II clinical efficacy and safety study (CRFB002AGB10), considered by the TGA to be supportive.
  - Appendices to the Summary of Clinical Efficacy and the Summary of Clinical Safety.
  - Lucentis Core Data Sheet (CDS), Version 1.2; statement on case report forms and individuallistings for clinical trials, Literature References.

3.2. Paediatric data

The sponsor stated that, based on a product specific waiver granted by the EMA on 22 December 2010 (EMEA-000527-PIP02-10), a paediatric development program is not in place for Lucentis for the treatment of visual impairment due to CNV secondary to PM. The grounds of the waiver are; '*All subsets of the paediatric population from birth to less than 18 years of age …. on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible.*'

3.3. Good clinical practice

The two studies submitted by the sponsor were conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

4. Pharmacokinetics

No new data.

5. Pharmacodynamics

No new data.

6. Dosage selection for the pivotal studies

There were no dose-ranging studies for the proposed indication.

7. Clinical efficacy

7.1. Pivotal efficacy study – RFB002F2301

7.1.1. Study design, objectives, locations and dates

7.1.1.1. Design

Study RFB002F2301 was a Phase III, randomised, double-masked, multi-national, multi-centre, active-controlled, 12 month study. It was designed to evaluate the efficacy and safety of two different dosing regimens of ranibizumab 0.5 mg compared with verteporfin (Visudyne) photodynamic therapy (vPDT) for the treatment of patients with visual impairment due to choroidal neovascularization (CNV) secondary to pathological myopia (PM). The study was sponsored by Novartis and was conducted in compliance with Good Clinical Practice (GCP). The study is identified by the acronym RADIANCE in the amended PI.

The study was undertaken in 20 countries and 76 sites. The participating countries (number of sites) were: Austria (2), Canada (2), France (5), Germany (10), Hong Kong (1), Hungary (2), India (5), Italy (5), Japan (14), Latvia (4), Lithuania (1), Poland (2), Portugal (1), Singapore (2), Slovakia (3), South Korea (2), Spain (4), Switzerland (3), Turkey (4), and the United Kingdom (4). The principal investigator was located at the University of Bern, Bern, Switzerland. The first patient visit was 11 October 2010 (first patient enrolled), and the last patient visit was 17 August 2012 (completed 12 months). The Clinical Study Report (CSR) was dated 30 November 2012 (final content) and was based on the 12 month data from the completed study.

7.1.1.2. Objectives

The primary objective of the study was -

- To demonstrate the superior efficacy of ranibizumab 0.5 mg, driven by stabilization and/or by disease activity re-treatment criteria, compared with vPDT as assessed by the difference between the average level of best-corrected visual acuity (BCVA, letters) over all monthly post-baseline assessments from Month 1 to Month 3 and the Baseline level of BCVA.

The secondary objectives of the study were -

- Key secondary objective: To demonstrate non-inferiority of ranibizumab 0.5 mg driven by disease activity re-treatment criteria versus ranibizumab 0.5 mg driven by stabilization criteria as assessed by the difference between the average level of BCVA (best corrected visual acuity; letters) over all monthly post-baseline assessments from Month 1 to Month 6 and the Baseline level of BCVA.
- To compare the efficacy of the two ranibizumab treatment groups as assessed by the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from Month 1 to Month 12 and the Baseline level of BCVA, based on the time course of BCVA changes from Baseline.
- To compare the proportion of patients with ≥10 and ≥15 letters gain or reaching ≥ 84 letters, and ≥10 and ≥15 letters loss for each month between treatment groups.
- To evaluate the time course of Central Retinal Thickness (CRT) changes from Baseline.
- To compare the proportion of patients with presence of active leakage over time up to Month 12.

- To assess the proportion of patients treated with ranibizumab by visit and to assess the number of ranibizumab re-treatments from Baseline to Month 2, Month 5 and Month 11 in the 0.5 mg ranibizumab treatment groups.
- To compare the safety and tolerability of each of the two regimens with 0.5 mg ranibizumab versus vPDT, and between the ranibizumab 0.5 mg treatment regimens, at Month 3, Month 6 and Month 12.

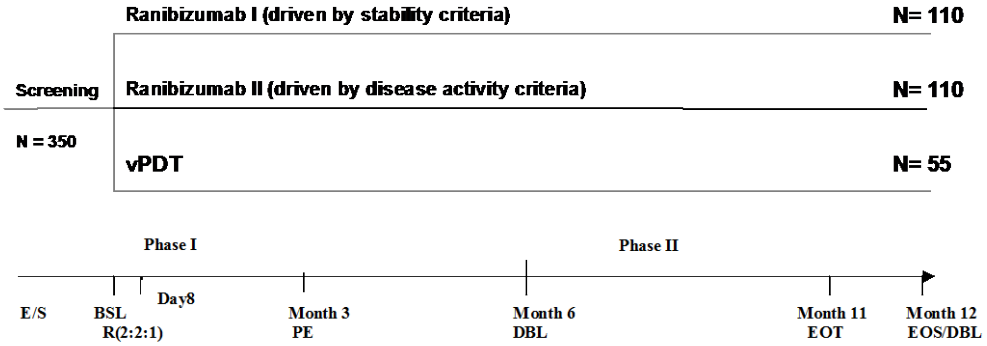
The exploratory objectives of the study were -

- [information redacted]
- To compare the clinical response of both ranibizumab 0.5 mg dosing regimens versus vPDT as assessed by the efficacy outcome measures in different clinical types of macular (subfoveal, juxtafoveal and extrafoveal) and peripapilar CNV lesions related to PM.
- To assess the impact on patient functioning and quality of life (QoL) supported by ranibizumab 0.5 mg versus vPDT as assessed by the National Eye Institute Visual Function questionnaire 25 (NEI-VFQ-25) and Euro Quality of Live Questionnaire 5 (EQ-5D), and the amount of work absence, work presence and daily activity impairment attributable to the ocular health status through the Work Productivity and Activity Impairment Questionnaire General Health (WPAI-GH).

7.1.1.3. Investigational plan

The study design is provided below in Figure 1.

Figure 1. CRFB002F2301 – Investigational plan.



BSL (baseline)
E (enrollment) S (screening)
PE (primary endpoint)
EOT (end of treatment)
EOS (end of study)
DBL (database lock)
vPDT- (Verteporfin photodynamic therapy)

There were two periods in the study: **screening period** (day -14 to baseline) – at Visit 1, after informed consent was signed, patients were assessed for eligibility; and **treatment period** (from Baseline, Visit 2 to Month 12, Visit 15) – eligible patients were randomised to one of the three treatment groups (2:2:1), ranibizumab by stabilization (Group I), ranibizumab by disease activity (Group II), and vPDT (Group III); the first dose of study medication was administered at Visit 2 and patients were treated up to Month 11. In the vPDT treatment group, treatment with ranibizumab 0.5 mg as a treatment option was allowed from Month 3 in case of disease activity.

Considering the expected effects of ranibizumab 0.5 mg and vPDT, the two primary comparative efficacy analyses were performed at Month 3 (that is, Group I versus III; Group II versus III). The pairwise analyses of efficacy and safety of the two ranibizumab 0.5 mg treatment groups were then evaluated at the completion of the 6-month study period (that is, the first time point

considered relevant to assess ranibizumab exposure in Groups I and II), and then at the completion of the 12 month study period (that is, long-term follow up).

The study was divided into two consecutive phases, and a database lock (DBL) occurred after each phase: **Phase I** was from Day 1 (Baseline) to Month 6; and **Phase II** was from Month 6 to Month 12. After all patients completed the Month 6 visit or discontinued prior to Month 6 the database was locked and the efficacy analyses (including the analyses of the primary endpoint and the key secondary endpoint) and the safety analyses were conducted. The results of these analyses were used in regulatory communication with health authorities, but otherwise not disseminated. The clinical team was unmasked after the Month 6 DBL. However, masking was maintained at the site level until the Month 12 DBL. Patients continued in the same designated treatment group until the closure of the study with the last assessment performed at visit 15 (Month 12).

Patients could voluntarily withdraw from the study for any reason at any time. Patients could also discontinue treatment because of the appearance of a new health condition suspected to require appropriate care or require medications prohibited by the protocol, unacceptable adverse events (AEs), refusal to continue treatment, or at the investigator's discretion based on his/her clinical judgment. If a patient elected to stop treatment, the patient was encouraged to continue in the study and to return for assessment at the remaining visits up to and including Visit 15. Patients who experienced a transient ischemic attack (TIA) or a stroke during the study were required to discontinue treatment with the study drug. The study included standard clinical trial procedures for following up patients who prematurely discontinued.

> Comment: The pivotal clinical study report (CSR) refers to 'several available publications' suggesting 'that patients with myopic CNV treated with intravitreal injections of 0.5 mg ranibizumab have a mean gain of 10 to 15 letters in VA within the first year of treatment achieved with an average of 1.5 to 3.8 injections'. Furthermore, the CSR commented that these publications also revealed that rapid improvement in VA in patients with myopic CNV occurred mostly within the first three-months of treatment, and was mirrored by improvement in the anatomical changes associated with the condition 'such as active leakage of the anomalous vasculature, subretinal fluid and hemorrhage'.
>
> The CSR stated that 'the rationale for the choice of dose for intravitreal injection of 0.5 mg ranibizumab' was based on data from the AMD and RVO pivotal trials showing that this dose had the 'most favorable risk/benefit' for treatment of these conditions. The CSR also notes that 'evidence from the AMD, DME, and RVO studies suggested that there were individual differences in the re-treatment need and responses, thus to allow for a balance of efficacy/safety/treatment burden for patients, an individualized ranibizumab treatment regimen was chosen for each of the two alternative ranibizumab treatment groups (from Month 2, or Month 1, respectively in Groups I and II). Flexible regimen and treatment was to be given only based on the assessment of VA stabilization (Group I) and/or disease activity (Group II) criteria'.
>
> The report also stated that vPDT is the only approved therapy to treat subfoveal CNV in patients with PM, and noted that there are less common types of non-subfoveal CNV (juxtafoveal, extrafoveal and peripapilar) secondary to PM that can cause VA for which there are no currently approved medications. The TGA approved indication for vPDT (Visudyne) is for the treatment of patients with predominately classic or occult subfoveal CNV due to AMD, or with subfoveal CNV caused by other macular disease. It can be inferred from the Australian Visudyne PI that subfoveal CNV caused by other macular disease includes PM. The Clinical Trial section of the Visudyne PI provides a description of the Verteporfin In Photodynamic Therapy of Pathologic Myopia study (VIP-PM study) under the heading of Other Macula Diseases (Pathologic Myopia).
>
> Overall, the rationale for the study design, including the choice of ranibizumab dose and

control treatment, is considered to be satisfactory.

7.1.1.4. Inclusion and exclusion criteria

The investigator assessed the eligibility of the patient and the study eye. If both eyes were eligible, the eye with the worse VA, as assessed at Visit 1, was selected for study treatment. The investigator could select the eye with better VA, based on medical reasons and according to local ethical requirements. Patients eligible for inclusion were required to fulfil all of the inclusion criteria prior to initial study drug administration. Patients fulfilling any of the exclusion criteria were not eligible for inclusion.

7.1.1.5. Study treatments

- Ranibizumab for intravitreal injection, 0.5 mg/0.05 mL.
- Visudyne®/verteporfin (vPDT) IV infusion (6 mg/m^2) for 10 minutes followed 15 minutes after the start of the infusion by a laser standard fluence (SF) rate of 600 mW/cm^2 delivered for 83 seconds with light dose of 50 J/cm^2.
- Ranibizumab sham consisted of an empty vial and needle free syringe with mimicking of the real IVT injection.
- vPDT sham consisted of an IV infusion of dextrose 5% solution followed by real PDT as for active vPDT treatment.
- In case of combination of vPDT and ranibizumab, the vPDT treatment was always administered before intravitreal injections. Verteporfin or verteporfin sham was administered at least 1 hour before ranibizumab or sham injection. It was recommended that the vPDT and ranibizumab treatments be performed on the same day. No patients received combination vPDT/ranibizumab treatment.
- Antimicrobials could be given based on clinical practice.

Study drug adjustments and other than protocol specified treatment interruptions were not permitted. There was no rescue medication/treatment.

7.1.1.6. Stabilization and disease activity criteria

If eligibility criteria were met, patients were randomised at Visit 2 (Day 1) in a 2:2:1 ratio to Group I, II, or III, respectively. During the study patients were monitored monthly (4 weeks ± 7 days) and were re-treated based on the stabilization and/or disease activity criteria defined below.

- **Stabilization criteria** were defined as no change in BCVA compared with the two preceding monthly evaluations.
- **Disease activity criteria** were defined as vision impairment attributable to intra-retinal or subretinal fluid or active leakage due to the CNV lesion secondary to PM as assessed by OCT and/or FA.

7.1.1.7. Treatment groups

- Group I (Ranibizumab I) – 0.5 mg ranibizumab re-treatment driven by BCVA stabilization criteria. Patients received 0.5 mg ranibizumab intravitreal injection at Day 1 and Month 1. The first time point to assess the BCVA stabilization criteria was Month 2, based on Baseline, Month 1 and Month 2 assessments. Dosing was stopped if the stabilization criteria for BCVA were fulfilled. Treatment was resumed with monthly injections when there was a loss of VA due to disease activity and continued until stable VA was reached again for three consecutive monthly assessments. In this group, 106 patients were randomised to treatment.

- Group II (Ranibizumab II) – 0.5 mg ranibizumab re-treatment driven by disease activity. Patients received intravitreal injection of 0.5 mg ranibizumab at Day 1. From Month 1, treatment was not given if no disease activity was seen, and treatment was given when disease activity criteria were observed. In this group, 116 patients were randomised to treatment.
- Group III (vPDT) – Patients received vPDT at Day 1 but no further active treatment with vPDT (or ranibizumab) was to be given at Month 1 or 2. From Month 3 to 12, the investigator had the following treatment options: (i) 0.5 mg ranibizumab; (ii) vPDT; or (iii) combination of 0.5 mg ranibizumab and vPDT. Treatment was given only when the disease activity criteria were observed. Of the 55 patients initially randomised to treatment with vPDT, 38 received treatment with ranibizumab alone from Month 3 though Month 12, 15 patients received treatment with vPDT alone from Month 3 through to Month 12, and 2 patients received treatment with ranibizumab prior to Month 3 (that is, protocol deviations). Out of the 15 patients who continued on vPDT from Month 3 through Month 12, 2 patients received a second vPDT treatment (1 at Month 3 and 1 at Month 5. Although from Month 3 through Month 12 the investigator could treat patients with vPDT, ranibizumab, or a combination of both, once a patient in Group III received treatment with ranibizumab no further treatments with vPDT were given to these patients during the course of the study (that is, no combinations of vPDT and ranibizumab were given). In total, there were 40 patients who were initially treated with vPDT and then received ranibizumab.
- In all three treatment groups masking with ranibizumab sham or PDT sham was to be performed.

7.1.1.8. Concomitant treatment

The following treatments were not allowed in the study: (i) systemic medications ethambutol, chloroquine, hydroxychoroquine, deferoxamine, phenothiazines, and tamoxifen; (ii) anticoagulant medications (other than aspirin) at study entry (Visit 1) and during the study; (iii) treatment with glitazones when newly started during the study; (iv) intraocular treatment with corticosteroids or any anti-VEGF other than study medication in the study eye; and (v) panretinal laser or focal laser photocoagulation with involvement of the macular area in the study eye. Standard of care (for example, vPDT) or other treatments, according to the investigator's practice for PM and other diseases in the fellow eye, was permitted at any time.

7.1.1.9. Efficacy variables and outcomes

7.1.1.9.1. Primary efficacy variable

The primary efficacy variable was the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from Month 1 to Month 3 (endpoint) and the Baseline level of BCVA. The primary efficacy variable aimed to assess the superiority of each of the ranibizumab 0.5 mg treatment regimens (Group I and Group III) compared with the active control vPDT treatment regimen (Group II).

> Comment: The primary efficacy endpoint is considered satisfactory. The indication is for the treatment of visual impairment and, consequently, improvement in BCVA is the most suitable and clinically relevant method of assessing the response to treatment of visual impairment due to CNV secondary to PM. There was no active control treatment after Month 3 as the protocol allowed patients randomised to vPDT (Group III) to be treated with ranibizumab after Month 3. The primary emphasis after Month 3 was the comparison between the two ranibizumab groups (Group I and Group II).

7.1.1.9.2. Secondary efficacy variables

a. The key secondary efficacy variable was the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from Month 1 to Month 6 and the Baseline level of BCVA. The key secondary efficacy endpoint aimed to assess

the non-inferiority of ranibizumab 0.5 mg driven by the disease activity re-treatment criteria (that is, Group II) compared with ranibizumab 0.5 mg driven by the VA stabilization re-treatment criteria (that is, Group I).

b. Other secondary efficacy variables based on the BCVA were: (i) change from Baseline in BCVA for all post-baseline visits (up to Month 12) to evaluate the time course of the treatment difference between the three treatments groups; (ii) proportion of patients who gained ≥1, ≥5, ≥10, or ≥15 letters compared to Baseline by post-baseline visits up to Month 12; (iii) proportion of patients who gained ≥10, ≥15 letters compared to Baseline, or reached 84 letters by post-baseline visit up to Month 12; and (iv) proportion of patients who lost ≥10, ≥15 letters compared with Baseline by post-baseline visit up to Month 12.

c. Other secondary efficacy variables based on OCT were: (i) subretinal fluid (volume scan, cross hair scan) with and without centre involvement; (ii) intraretinal oedema (volume scan, cross hair scan) with and without centre involvement; (iii) intraretinal cysts (volume scan, cross hair scan) with and without centre involvement; (iv) CRT (μm) total by OCT system, and ethnicity; (v) central foveal thickness (CFT; μm) total, by OCT system.

d. Other secondary efficacy variables based on FA as assessed by CRC were analysed at 12 months: (i) evidence of CNV and CNV leakage with and without centre involvement; (ii) area of lesion (mm^2); (iii) area of CNV (mm^3); and (iv) greatest linear dimension of entire CV lesion (μm).

Comment: The secondary endpoints are considered to be satisfactory. The key secondary efficacy variable is the main secondary endpoint testing the efficacy of ranibizumab for treatment of the proposed indication. This endpoint compared the two ranibizumab 0.5 mg dosing regimens (Group I versus Group II). Other efficacy variables based on the BCVA tested the long-term efficacy (12 months) of ranibizumab for treatment of the proposed indication. In addition to assessment of BCVA, the secondary efficacy variables also assessed changes in the anatomical abnormalities associated with CNV secondary to PM.

7.1.1.9.3. Efficacy assessment methods

a. Best corrected visual acuity (BCVA) - The BCVA was tested using the ETDRS VA testing protocol. VA measurements were taken in a sitting position at an initial test distance of 4 metres using ETDRS charts. The BCVA was assessed at every visit for the study eye, and the BCVA was assessed at Screening (Visit 1), Visit 6 and at Visit 15 for the fellow eye.

b. Optical coherence tomography (OCT) - OCT was assessed at all study visits, except Visit 3, in the study eye. In the fellow eye, OCT was assessed at Screening and Visit 15. The OCT assessments were performed by trained technicians at the study sites prior to study drug administration. The images were reviewed by a Central Reading Centre (CRC) to ensure a standardized evaluation. The CRC then transferred the data for the statistical analysis to the Contract Research Organization (CRO).

c. Colour fundus (CF) photography and fluorescein angiography (FA) - FA was performed after CF photography to assess the choroid and retinal vasculature. These assessments were performed by a trained technician at Screening and End of Study (EOS) visits for all patients in both eyes. Additional assessments for re-treatment from Month 1 to 11 were performed, if needed, in the study eye. CF photography and FA images were independently reviewed by the CRC to ensure standardized evaluation, and the data were then transferred to the CRO for statistical analysis.

Comment: The selected efficacy assessment methods are clinically relevant. In addition, the methods are standard for ophthalmological clinical trials involving assessment of the efficacy of medicines administered by IVT injection for the treatment of visual impairment

due to intraocular disease.

7.1.1.9.4. Randomisation and blinding methods

Each patient was uniquely identified in the study by a combination of centre and patient number. The centre number was assigned by Novartis, and the patient number was assigned by the investigator. The randomization numbers were generated using procedures to ensure that treatment assignment was unbiased and concealed from patients and investigator staff. A randomization list was produced by or under the responsibility of Novartis using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio (that is, 2:2:1 = Group I:II:III). The randomization scheme was reviewed and approved by a member of the Biostatistics Quality Assurance Group.

Treatment masking was maintained in all groups during the entire 12 month duration of the study, and emergency unmasking was to be undertaken only when considered essential for patient safety. The study included masked and unmasked investigators and their functions are outlined below.

The **assessing investigator** (masked to treatment assignment) performed the monthly clinical and ancillary assessments, and provided the following re-treatment assessments to the treating investigator:

- Patient status regarding stability according to the stabilization criteria (from Month 2 onwards): yes (stability +) /no (stability -).
- Patient status regarding disease activity according to the disease activity criteria (from Month 1 onwards): yes (DA +) /no (DA -).
- Treatment recommendation (TR) (from Month 3 onwards and only if there was 'disease activity= yes' (DA+), taking into account vPDT treatment guidelines): 'ranibizumab' or 'vPDT' or 'ranibizumab+ vPDT'.

The **treating investigator** (unmasked to treatment assignment) did not perform any study assessments, did not complete eCRFs, was not to be involved in any other aspects of the study and was not allowed to communicate details of the treatment to anyone. The treating investigator treated the patient based on the three re-treatment assessments provided by the assessing investigator and the randomised treatment group. The translation of the re-treatment assessments provided by the assessing investigator into the treatment arm specific applications to be performed by the treating investigator is outlined below:

- The stability assessment was only relevant for Group I (ranibizumab treatment by stability).
- The disease activity assessment was relevant for Group II (ranibizumab treatment by disease activity) from Month 1 onwards and for Group III (vPDT) from Month 3 onwards.
- The treatment recommendation was only relevant for Group III (vPDT) from Month 3 onwards if at the same time there was 'disease activity = yes (DA+)'.

For **masking purpose** there were both sham ranibizumab and sham vPDT applications. To ensure masking was maintained from Month 3 onwards when patients in Group III (vPDT) could receive ranibizumab, the site staff were provided with a study aid.

After randomization on Day 1, switching from one to another group was not allowed at any time. The patients were to remain in the designated group and were masked to the treatment until the conclusion of the study.

Patients, physicians and other site personnel performing assessments, and data analysts remained masked to the identity of the treatment from the time of randomization until DBL. Randomization data were kept strictly confidential until the time of unmasking, and were accessible only by the treating investigator. During and after DBL at Month 6, the masked study site personnel and patients remained masked to the treatment assignment until the conclusion

of the study. Since the two study medications had very different appearances and routes of administration, masking during treatment administration was necessary to minimize the potential for patient and investigator bias. To ensure masking, the entire vPDT and PDT sham devices were covered with aluminium foil by the study staff at the sites in order to avoid recognition of the medications.

7.1.1.10. Analysis populations

- The **Randomised Set** consisted of all randomised patients.
- The **Full Analysis Set (FAS)** consisted of all randomised patients who received at least one application of study treatment and had at least one post-baseline BCVA assessment in the study eye. Following the intent-to-treat principle, patients were analysed according to the treatment assigned. No data were excluded from the FAS analyses because of protocol deviations.
- The **Per Protocol Set at Month 3 (PPSM3)** consisted of all patients in the FAS who received study treatment as randomised and completed Months 1 to 3 of the trial without clinically significant protocol deviations.
- The **Per Protocol Set at Month 6 (PPSM6)** consisted of all patients in the FAS who received study treatment as randomised and completed Months 1 to 6 of the trial without clinically significant protocol deviations.
- The **Safety Set** consisted of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment. Patients were analysed by treatment received.

7.1.1.11. Sample size

With 110 patients in each of the ranibizumab groups and 55 patients in the vPDT group, based on pair-wise treatment group comparisons using Cochran-Mantel Haenszel (CMH) tests at multiple one-sided 0.001 (Hochberg procedure), and assuming a treatment difference of 8 letters between each of the ranibizumab groups and vPDT and standard deviation (SD) of 10 letters, the power to reject at least one of the hypotheses H01 or H02 is ≥ 91% (see description of Statistical Methods, below, for definition of H01 and H02). It was assumed that the stratification planned in the primary analyses had a tendency to further increase the power, and that the impact by drop-outs at Month 3 was negligible. The assumptions for the sample size calculation were based on published studies.[4,5,6,7,8] It was further assumed that the SD for the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from Month 1 to Month 3 was approximately 85% of the SD for change from Baseline at Month 3 and Month 6.[7,8]

For the key secondary efficacy variable, assuming SD of 10,[7,8] and equal means for the two ranibizumab groups, then 110 patients per treatment group were sufficient to achieve a power of 91% to reject H03 (see description of Statistical Methods, below, for definition of H03).

> Comment: The assumptions relating to differences in VA on which the power calculations are based are considered to be reasonable. The studies referred to in the CSR relating to the calculation of the sample size calculation have been examined and are considered to be appropriate.[4,5,6,7,8]

7.1.1.12. Statistical methods

7.1.1.12.1. Primary efficacy variable

The primary efficacy variable was the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from Month 1 to Month 3 (endpoint) and the Baseline level of BCVA. The primary efficacy variable was compared between treatment groups as follows:

- The one-sided hypotheses (H0 = null, HA = alternate),
- H01: μ Ranibizumab-Group I minus μ vPDT ≤ 0 versus HA1: μ Ranibizumab-Group I minus μ vPDT > 0,
- H02: μ Ranibizumab-Group II minus μ vPDT ≤ 0 versus HA2: μ Ranibizumab-Group II minus μ vPDT > 0,

were tested at multiple alpha-level 0.001 using the Hochberg procedure, where μ Ranibizumab-Group I was the mean value of the primary variable for treatment Group I, μ Ranibizumab-Group II was the mean value for treatment Group II, and μ vPDT was the mean value for the vPDT treatment Group III. Hochberg procedure superiority was to be claimed if the corresponding one-sided p-value was ≤0.001/2=0.0005 or if both one-sided p-values were ≤0.001.

Primary analysis

The comparisons were performed using the stratified CMH test with the observed values as scores. Stratification was based on categories of Baseline BCVA (≤60 letters versus >60 letters), as the VIP-PM study[7,8] suggested that improvement in BCVA was correlated with Baseline BCVA. The cut-point of 60 represents the approximate median Baseline BCVA level. The CMH tests were carried out in a pair-wise manner comparing each individual ranibizumab group with the vPDT group. The tests produced two-sided p-values showing whether ranibizumab (Groups I or II) or vPDT (Group III) had the better score. For each comparison, if the direction of the observed difference supported the superiority outcome (for example, mean difference >0), the two sided p-value was converted to a one sided p-value by dividing by two. Otherwise, the one-sided p-value was calculated as 1 - (the two-sided p-value divided by two).

The primary analysis was performed for FAS and employed a modified Last Observation Carried Forward (LOCF) approach in which missing values occurring between observed values were to be replaced by the mean of the last observation before and the first observation after the missing value. In addition, the impact of missing data were assessed using the standard LOCF approach (that is, missing values replaced by carrying forward the previous non-missing post-baseline value), and the first observation carried back (FOCB) approach (that is, missing values replaced by carrying back the first available non-missing post-baseline values).

Supportive analyses

The primary variable was also assessed by supportive analyses using parametric statistical methods. The two-sided 95% confidence interval (CI) for the absolute BCVA and the average changes in BCVA and the corresponding pair-wise difference between treatments was calculated using the least square means (LSMs) from an analysis of variance (ANOVA) model with treatment and Baseline BCVA category (≤ 60 letters versus > 60 letters) as factors. Additionally an un-stratified CMH tests was conducted and its p-value was presented. For sensitivity purposes, the analyses of the primary variable (CMH and ANOVA) were repeated for the FAS and the PPSM3 using a standard LOCF approach and a FOCB approach for any missing values. Additionally, analyses using the observed values were carried out for both populations.

The primary analysis was repeated with following subgroups: age category (<45, 45 to <55, 55 to <65, ≥65 years); sex (male, female); race (Caucasian, Asian, Other); ethnicity (Japanese, non-Japanese); Baseline BCVA (<45, 45 to <60, 60 to <73, ≥73 letters); Baseline axial length (<28 mm, 28 to <30 mm, ≥30 mm); Baseline location of CNV (subfoveal, non subfoveal, missing); and Baseline location of CNV subtype (subfoveal, juxtafoveal, extrafoveal, margin of the optic disc, missing, can't grade, not applicable). Subgroup analyses were performed on the FAS using modified LOCF and the observed values.

7.1.1.12.2. Key secondary efficacy variable

The key secondary efficacy variable was the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from Month 1 to Month 6 and the Baseline level of BCVA compared between ranibizumab treatment groups (Group I versus Group II).

The following hypotheses (H03 and HA3) in the FAS with modified LOCF) were tested:

H03: μ Ranibizumab-Group II **minus** μ Ranibizumab-Group I ≤ -5 letters versus HA3: μ Ranibizumab-Group II **minus** μ Ranibizumab-Group I > -5 letters at a one-sided alpha level 0.025, if H01 and H02 were rejected, otherwise H03 was to be considered to be not rejected. This procedure kept the multiple one-sided alpha-level 0.001 for testing H01, H02 and the multiple one-sided alpha-level of 0.025 for H01, H02, and H03. The set of primary hypotheses was considered to be {H01, H02}, and the set of key secondary hypotheses was considered to be {H03}.

The comparison according to H03 was based on a stratified CMH test using the observed key secondary variable values as scores. The two sided 95% CI of the average changes in BCVA and the corresponding pairwise difference between both treatments groups was calculated using LSMs for treatment differences from an ANOVA model with treatment and baseline BCVA category (≤60 letters versus >60 letters) as factors. These analyses were performed for the FAS and PPSM6.

The pre-specified non-inferiority margin of 5 letters was based on health authority feedback related to the Visudyne project in 2008.

For sensitivity purposes, the analysis of the key secondary efficacy variable was performed also with the PPSM6 using LOCF for the imputation of missing values. The analyses were repeated in both analysis sets based on observed data, standard LOCF and FOCB.

> Comment: The key secondary efficacy variable was assessed by a pairwise comparison between the two ranibizumab treatment groups, and pairwise comparisons between the two ranibizumab treatment groups and the two vPDT treatment groups (that is, with and without ranibizumab) were not part of the assessment of this variable.

7.1.1.12.3. Other secondary efficacy variables

For continuous and ordered categorical variables, changes from Baseline were compared between treatment groups using ANOVA models and/or stratified CMH/exact Fisher tests. Stratification for BCVA followed the approach described for the primary analysis. All secondary analyses were performed on the FAS based on observed data and either a modified LOCF approach for BCVA endpoints or a standard LOCF approach for other endpoints. Statistical testing results (p-values) except for the primary and key secondary objective were not adjusted for multiple testing and are to be interpreted as descriptive.

> Comment: The p-values for all secondary efficacy endpoints, apart from the key secondary efficacy endpoint, are descriptive (nominal) rather than confirmatory, due to no adjustment of the significance level for multiple testing.

7.1.1.12.4. Interim analysis

No interim analyses were performed. However, as specified in the protocol the results of this study were analysed at two time points (that is, after the Month 6 DBL [Day 1 to Month 3 and Day 1 to Month 6 analyses]), and after the Month 12 DBL [Day 1 to Month 3, Day 1 to Month 6 and Day 1 to Month 12 analyses]).

7.1.1.13. Participant flow

Out of the 334 patients screened, 277 patients were randomised 2:2:1 to the following treatment groups: 106 patients to Group I (ranibizumab by stabilization), 116 patients to Group II (ranibizumab by disease activity), and 55 patients to Group III (vPDT). Overall, 276 (99.6%)

randomised patients completed 3 months, 274 (98.9%) completed 6 months and 267 (96.4%) completed 12 months. No patients discontinued the study due to AEs. No patients in Group III discontinued the study prior to Month 12, while 6 (5.7%) patients in Group II and 4 (3.4%) patients in Group II discontinued the study prior to Month 12. Patient disposition in the randomised population is summarised below in Table 1.

Table 1. CRFB002F3201 – Patient disposition; randomised set.

	Ranibizumab 0.5 mg		vPDT	Total
Disposition Reason	Group I by stabilization n (%)	Group II by disease activity n (%)	Group III n (%)	Total n (%)
Screened				334
Randomized	106 (100.0)	116 (100.0)	55 (100.0)	277 (100.0)
Completed 3 Months	105 (99.1)	116 (100.0)	55 (100.0)	276 (99.6)
Discontinued study prior to Month 3	1 (0.9)	0	0	1 (0.4)
Protocol deviation	1 (0.9)	0	0	1 (0.4)
Completed 6 Months	103 (97.2)	116 (100.0)	55 (100.0)	274 (98.9)
Discontinued study prior to Month 6	3 (2.8)	0	0	3 (1.1)
Subject withdrew consent	1 (0.9)	0	0	1 (0.4)
Lost to follow-up	1 (0.9)	0	0	1 (0.4)
Protocol deviation	1 (0.9)	0	0	1 (0.4)
Completed study (12 months)	100 (94.3)	112 (96.6)	55 (100.0)	267 (96.4)
Discontinued study prior to Month 12	6 (5.7)	4 (3.4)	0	10 (3.6)
Unsatisfactory therapeutic effect	1 (0.9)	0	0	1 (0.4)
Subject withdrew consent	1 (0.9)	2 (1.7)	0	3 (1.1)
Lost to follow-up	3 (2.8)	1 (0.9)	0	4 (1.4)
Protocol deviation	1 (0.9)	1 (0.9)	0	2 (0.7)

7.1.1.14. Major protocol violations/deviations

Overall, a total of 54 patients (19.5%) were recorded with at least one protocol deviation: Group I, 18 (17.0%); Group II, 22 (19.0%); and Group III, 14 (25.5%). Protocol deviations considered to be clinically significant were recorded in 19 (6.9%) patients: Group I, n=7 (6.6%); Group II, n=9 (7.8%); and Group III, n=3 (5.5%). The majority of clinically significant protocol deviations related to study medication deviations (that is, under-treatment or over-treatment in the first 3 months in 6 and 8 patients, respectively; under-treatment or over-treatment from Month 3 to Month 12 in 1 and 2 patients, respectively). Overall, clinically significant inclusion criteria deviations were reported in 7 patients.

> Comment: It is considered that the clinically significant protocol deviations reported in the study are unlikely to have significantly affected the statistical analyses of the primary and key secondary efficacy endpoints.

7.1.1.15. Baseline data

7.1.1.15.1. Demographics

The mean (SD) age of all randomised patients (n=277) was 55.5 (±13.94) years (range: 18 to 87 years), and 19.9% of all patients were younger than 45 years. Most of the patients were female (75.5%). The majority of patients were Caucasian (58.5%), with the remainder being mostly Asian (41.2%). Of the Asian patients, 18.1% were Japanese, 9.7% were Indian (Indian subcontinent), and 6.5% were Chinese. Baseline demographics were well balanced in all 3 treatment groups.

7.1.1.15.2. Ocular characteristics of the study eye

The ocular characteristics of the study eye at baseline in the randomised set included BCVA, IOP, axial length, and refraction-sphere (dioptres).

Baseline VA was comparable in all 3 treatment groups with mean BCVA scores ranging from 54.7 to 55.8 letters, with the mean (SD) score in all patients being 55.4 (13.11) and ranging from

8 to 83. In the total population (n=277), 21.7% had baseline BCVA < 45 letters, 39.7% had baseline BCVA 45 to < 60, 30.7% had baseline BCVA 60 to < 73 letters, and 7.9% had baseline BCVA ≥ 73 letters. In each of the three treatment groups approximately 70% of patients had baseline BCVA > 45 letters.

The mean (SD) axial length at baseline in the total population was 29.07 (1.892) mm, and ranged from 22.2 mm to 36.1 mm. The mean axial length was similar in the three treatment groups (28.75 to 29.37 mm). However, the distribution of the axial lengths < 28, 28 to < 30, and ≥ 30 mm differed in the three treatment groups. One patient in Group I presented with the required PM signs except for an axial length of ≥ 26 mm (presented with axial length 22.2 mm, reported as a protocol deviation).

The mean (SD) refraction-sphere (dioptres) in the total population was 12.502 (5.0102), and ranged from 6.00 to 30.00. The mean refraction-sphere (dioptres) was similar in the three treatment groups (11.550 to 13.727). However, the distribution of the refraction-sphere (dioptres) < 10, 10 to < 20, and ≥ 20 differed in the three treatment groups.

7.1.1.15.3. Ocular characteristics of the study eye – evaluated by OCT and FA/CF.

The ocular characteristics of the study eye at baseline as evaluated by OCT and FA/CF assessed were central retinal thickness (CRT), central foveal thickness (CFT), CNV evidence, CNV location, subretinal fluid (volume scan) and intraretinal oedema (volume scan). There were differences in the mean CRT and the mean CFT in the three treatment groups. However, the other anatomical parameters were comparable across the three treatment groups. The majority of all patients were diagnosed as having subfoveal CNV (68%), with juxtafoveal and extrafoveal CNV being diagnosed in 23.8% and 4.0% of all patients, respectively.

7.1.1.15.4. Medical history and active medical conditions

The proportion of patients with relevant medical history of the study eye was comparable in patients in the ranibizumab groups (Group I, 35.8%; Group II, 36.2%), and higher in patients in the vPDT group (43.6%) than in both ranibizumab groups. The most frequent ocular medical conditions (≥3% of all patients) were cataract operation (14.1%), cataract (8.7%), eye laser surgery (3.2%), and keratomileusis (3.2%). The proportion of patients with active ocular medical conditions of the study eye were comparable in the three treatment groups (Group I, 37.7%; Group II, 37.1%; and Group III, 36.4%). Myopia and CNV due to PM were both inclusion criteria and, therefore, according to the protocol not required to be entered into the medical history CRF. The most commonly reported active ocular medical condition, other than the disease of interest, was cataract which was reported in 7.2% patients in the total population (Group I, 5.7%; Group II, 7.8%; and Group III, 9.1%). Other active ocular medical conditions in the study eye, other than the disease of interest, occurring in ≥ 1.0% of the total population were AMD (4.7%), dry-eye (3.2%), allergic conjunctivitis (2.5%), glaucoma (2.5%), malignant myopia (2.2%), and arteriosclerotic retinopathy (1.1%).

Overall, 62.8% of all patients were reported with an active non-ocular medical condition, most frequently related to vascular disorders (28.2%), musculoskeletal and connective tissue disorders (18.1%), and metabolism and nutrition disorders (15.5%). A total of 72 (26.0%) patients were reported with hypertension, 12 (4.3%) patients with diabetes mellitus, 4 (1.4%) patients with myocardial ischemia and 1 (0.4%) patient with cerebral ischaemia.

7.1.2. Results for the primary efficacy outcome

The primary efficacy variable was the average change in BCVA from Baseline to Month 1 through Month 3 in the three treatment groups (see Table 2, below).

Table 2. CRFB002F2301 – Visual acuity of the study eye (letters), average change from baseline to Month 1 through Month 3; FAS (modified LOCF).

		Ranibizumab 0.5 mg		vPDT
		Group I by stabilization	Group II by disease activity	Group III
Parameter	Statistic	N=105	N=116	N=55
Baseline	n	105	116	55
	Mean (SD)	55.4 (13.43)	55.8 (12.59)	54.7 (13.84)
	SE	1.31	1.17	1.87
	Median	57.0	57.0	57.0
	Min - Max	23 - 83	27 - 79	8 - 77
Average Month 1 to Month 3	n	105	116	55
	Mean (SD)	66.0 (12.98)	66.4 (12.28)	56.9 (14.49)
	SE	1.27	1.14	1.95
	Median	69.0	69.2	58.3
	Min - Max	12.0 - 86.0	30.7 - 90.0	10.3 - 91.0
Average change from baseline	n	105	116	55
	Mean (SD)	10.5 (8.16)	10.6 (7.26)	2.2 (9.47)
	SE	0.80	0.67	1.28
	Median	10.3	10.0	1.7
	Min - Max	-19.3 - 31.0	-8.3 - 32.0	-24.7 - 24.3
Comparison vs vPDT	Difference in LS means (1)	8.5	8.6	
	95% CI for difference (1)	(5.8, 11.2)	(6.1, 11.1)	
	p-value (2)	<0.00001	<0.00001	

Notes: n is the number of patients with a value for both baseline and average Month 1 to Month 3. Stratified analysis includes baseline visual acuity (<=60, >60 letters) as factors. (1) Differences in LSM and the two-sided 95% CIs are estimated from pairwise ANOVA (stratified) model. (2) One-sided p-values for treatment difference are derived from the two-sided stratified CMH test using the row means score statistics.

The summary statistics and the sensitivity analyses for BCVA in the study eye (primary efficacy endpoint) obtained in the FAS (observed, LOCF, FOCB) and the PPSM3 (modified LOCF, observed, LOCF, FOCB) have been examined and are consistent with the results reported in the FAS (modified LOCF) (that is, the primary analysis of the primary efficacy endpoint).

> Comment: The primary objective of the study was met. Information provided in the submission, [information redacted] indicates that the 'Month 3 endpoint was designed [by the sponsor] for ethical reasons (higher efficacy is expected with ranibizumab treatment)', with investigator's being allowed to treat patients who had been randomised to vPDT with ranibizumab after the Month 3 endpoint. This justification is considered to be reasonable. Both ranibizumab treatment groups demonstrated statistically significant superior efficacy compared with vPDT for mean average change in BCVA from Baseline to Month 1 through Month 3. The mean average change in BCVA score of the study eye in the three treatment groups was 10.5 letters (Group I), 10.6 letters (Group II) and 2.2 letters (Group III). For both pairwise comparisons (that is, Group I versus Group III, Group II versus Group III), the mean average change from Baseline in BCVA of the study eye was statistically significantly greater in patients treated with ranibizumab compared with patients treated with vPDT (that is, one-sided nominal $p < 0.00001$ for both pairwise comparisons; and confirmatory one-sided p-value of ≤0.001, adjusted for multiplicity, for both pairwise comparisons). The difference in the LSM in BCVA (letters) between ranibizumab (Group I) and vPDT (Group III) was 8.5 (95% CI: 5.8, 11.2), and between ranibizumab (Group II) and vPDT (Group III) was 8.6 (95% CI: 6.1, 11.1). The differences in BCVA for both pair-wise comparisons are considered to be clinically significant as they were both ≥ 8 letters (see assumptions for calculation of sample size).

7.1.3. Key secondary efficacy outcome

The key secondary efficacy variable was the average level of BCVA over all monthly post-baseline assessments from Month 1 to Month 6 compared with the Baseline level of BCVA, in the two ranibizumab treatment groups. The results of the non-inferiority comparison between the two ranibizumab treatment groups for the mean average change in BCVA of the study eye from Baseline to Month 1 through Month 6 are summarised below in Table 3.

Table 3. CRFB002F2301 – Visual acuity of the study eye (letters), average change from baseline to Month 1 through Month 6; FAS (modified LOCF).

		Ranibizumab 0.5 mg	
		Group I by stabilization	Group II by disease activity
Parameter	**Statistic**	**N=105**	**N=116**
Baseline	n	105	116
	Mean (SD)	55.4 (13.43)	55.8 (12.59)
	SE	1.31	1.17
	Median	57.0	57.0
	Min - Max	23 - 83	27 - 79
Average Month 1 to Month 6	n	105	116
	Mean (SD)	67.3 (12.40)	67.5 (12.34)
	SE	1.21	1.15
	Median	70.3	69.9
	Min - Max	17.5 - 86.0	31.5 - 90.0
Average change from baseline	n	105	116
	Mean (SD)	11.9 (8.81)	11.7 (8.24)
	SE	0.86	0.76
	Median	11.2	11.7
	Min - Max	-18.7 - 34.5	-9.7 - 35.7
Comparison vs Group I	Difference in LS means (1)		-0.1
	95% CI for difference (1)		(-2.2, 2.0)
	p-value (2)		<0.00001

- n is the number of patients with a value for both baseline and average Month 1 to Month 6.
- Stratified analysis includes baseline visual acuity (<=60, >60 letters) as a factor.
(1) Differences in LS means and the two-sided 95% CIs are estimated from pairwise ANOVA (stratified) model.
(2) This p-value for non-inferiority is from a CMH test (stratified), is one-sided and based on the null hypothesis: Group II by disease activity is not more than 5 letters worse than Group I by stabilization, against the alternative hypothesis: Group II by disease activity is more than 5 letters worse than Group I by stabilization.

The summary statistics and the sensitivity analyses for BCVA in the study eye from baseline through to Month 1 through Month 6 (key secondary efficacy endpoint) obtained in the FAS (observed, LOCF, FOCB) and the PPSM6 (modified LOCF, observed, LOCF, FOCB) have been examined and are consistent with the results reported in the FAS (modified LOCF) (that is, the primary analysis of the primary efficacy endpoint).

> Comment: The key secondary objective of the study was met. Ranibizumab Group II was statistically non-inferior to ranibizumab Group I with respect to mean average change from Baseline in BCVA of the study eye to Month 1 through Month 6. The mean average change from baseline from Month 1 to Month 6 in BCVA was similar in patients treated with ranibizumab in Group 1 (stabilization) and patients treated with ranibizumab in Group II (disease activity) (11.9 and 11.7 letters, respectively; nominal one-sided $p < 0.00001$). The mean average change in Group I was statistically non-inferior compared with Group II (that is, one-sided $p < 0.025$, adjusted for multiplicity of testing of primary and key secondary efficacy outcomes). The difference in the LSM for the BCVA between Group I and II of -0.1 (95% CI: -2.2, 2.0) letters is considered to be clinically insignificant.

7.1.4. Other secondary efficacy endpoint outcomes

1. *Average change in visual acuity up to Month 12:* The improvement in BCVA seen at Month 6 in patients treated with ranibizumab in both Groups I and II was maintained up to Month 12. The average BCVA from Month 1 to Month 12 was 68.3 letters in both Group I and

Group II. The mean average change in BCVA from Baseline to Month 1 through Month12 was 12.8 letters and 12.5 letters in Group I and Group II, respectively. Patients in Group III (vPDT) reached an average BCVA of 61.1 letters from Month 1 through Month 12 and a mean average change from Baseline of 6.4 letters (that is, in this group patients received re-treatment with ranibizumab or vPDT from Month 3 through Month 12). In Group III, there were 40 patients who were initially treated with vPDT and then re-treated with ranibizumab from Month 3 through Month 12. In these patients, At Month 12, the mean BCVA improvement from Baseline through Month 12 was 10.4 letters. This outcome is comparable to the results in both ranibizumab treatment arms (that is, Group I [12.8 letters]; Group II [12.5 letters]).

2. *Mean change from baseline in visual acuity over time:* Rapid VA improvement with ranibizumab was observed at Month 1 in Groups I and II and most of improvement in VA was reached by Month 2. During the following months and up to Month 12 the gain in VA was maintained at the same or a slightly increased level compared to Month 3. The mean VA – time curves for the two ranibizumab groups were almost superimposable.

3. *Change from baseline in visual acuity at Month 3, Month 6, and Month 12:* At Month 3, improvement of mean BCVA was higher in patients randomised to ranibizumab (Group I: 12.1 letters; Group II: 12.5 letters) than in patients randomised to vPDT (Group III: 1.4 letters). This effect was maintained throughout the study resulting in a mean BCVA improvement of 13.7 letters and 12.7 letters (at Month 6) and of 13.8 letters and 14.4 letters (at Month 12) for patients treated with ranibizumab according to stability (Group I) and disease activity (Group II), respectively. The mean change from Baseline in BCVA at Month 6 and Month 12 was 7.9 letters and 9.3 letters, respectively, in patients in Group III.

4. *Categorized gain from baseline in VA (≥ 15 or ≥ 10 letters or reached a BCVA of ≥ 84 letters):* The proportion of patients who gained ≥15 letters (or reached a BCVA of ≥84 letters) from Baseline increased continuously throughout the treatment as shown for the FAS (modified LOCF): 38.1%, 43.1% and 14.5% (up to Month 3), 46.7%, 44.8% and 27.3% (up to Month 6) and 53.3%, 51.7% and 32.7% (up to Month 12) of patients in Groups I, II and III, respectively. Similarly, a gain of ≥10 letters (or reached a BCVA of ≥84 letters) was seen in 61.9%, 65.5%, and 27.3% of patients up to Month 3, 71.4%, 64.7%, and 45.5% up to Month 6, and 69.5%, 69.0%, and 49.1% up to Month 12, in Groups I, II, and III, respectively.

5. *Categorized loss from baseline in VA (≥ 15 or ≥ 10 letters):* The proportion of patients who lost ≥15 letters from Baseline in the FAS (modified LOCF) was 1.9%, 0% and 7.3% (up to Month 3), 0%, 0.9%, and 3.6% (up to Month 6), and 1.9%, 0.9%, and 3.6% (up to Month 12), in Groups I, II and III, respectively. The proportion of patients (Groups I, II, III, respectively) who lost ≥ 10 letters was 1.9%, 0.9%, and 16.4% up to Month 3, 1.9%, 2.6%, and 3.6% up to Month 6, and 4.8%, 1.7%, and 3.6% up to Month 12.

6. *Change in central retinal thickness (CRT) over time:* In Group I and II, mean changes from Baseline to Month 3 in CRT for the FAS (LOCF) were -61.0 µm and -77.6 µm, respectively, compared with -12.0 µm in Group III (vPDT). From Baseline to Month 6, mean changes in CRT were -66.1 µm, -74.8 µm, and -51.5 µm in Group I, II and III, respectively, and mean changes from Baseline to Month 12 were -66.6 µm, -71.3 µm, and -60.8 µm in Groups I, II, and III, respectively. Patients randomised to vPDT showed a decrease in CRT from Month 3 onwards, suggesting that this was due to ranibizumab as patients were allowed to receive this drug after Month 3. The mean change from Baseline in CRT over time in the FAS (LOCF) for each of the three treatment groups was summarised.

7. *Change in central foveal thickness (CFT) over time:* Mean changes from Baseline in CFT for the FAS (LOCF) in Group I, II, and III were -62.6 µm, -74.3 µm, and -18.6 µm at Month 3, -68.2 µm, -79.8 µm, and -57.0 µm at Month 6, and -68.4 µm, -75.1 µm, and -62.6 µm at Month 12, respectively. The changes in CFT over time in the three groups were consistent with the changes in CRT over time.

8. *Subretinal fluid (volume scan):* The proportion of patients with subretinal fluid at Baseline (Group I, 35.2%, 37/105; Group II, 40.5%, 47/116; Group III, 34.5%, 19/55) decreased continuously in all treatment groups (FAS/LOCF). At Month 3, subretinal fluid in the study eye was diagnosed as definite in 5.7% (n=6), 3.4% (n=4), and 16.4% (n=9) of patients in Groups I, II, and III, respectively, at Month 6 in 4.8% (n=5), 6.0% (n=7), and 0% (n=0) of patients in Groups I, II, and III, respectively, and at Month 12 in 3.8% (N=4), 4.3% (N=5), and 1.8% (n=1) of patients in Groups I, II, and III, respectively.
9. *Intraretinal oedema (volume scan):* The proportion of patients with intraretinal oedema at Baseline (Group I, 84.8%, 89/105; Group II, 79.3%, 92/116; Group III, 87.3%, 48/55) decreased continuously in all treatment groups (FAS/LOCF). At Month 3, intraretinal oedema in the study eye was diagnosed as definite in 34.3% (n=36), 34.5% (n=40), and 54.5% (n=30) of patients in Groups I, II, and III, respectively, at Month 6 in 16.2% (n=17), 16.4% (n=19), and 14.5% (n=8) of patients in Groups I, II, and III, respectively, and at Month 12 in 2.9% (n=3), 4.3% (n=5) and 1.8% (n=1) of patients in Groups I, II, and III, respectively.
10. *Intraretinal cysts (volume scan):* The proportion of patients with intraretinal cysts at Baseline (Group I, 27.6%, 29/105; Group II, 27.6%, 32/116; Group III, 18.2%, 10/55) decreased continuously in all treatment groups (FAS/LOCF). At Month 3, intraretinal cysts in the study eye were diagnosed as definite in 14.3% (n=15), 14.7% (n=17), and 9.1% (n=5) of patients in Groups I, II, and III, at Month 6 in 12.4% (n=13), 6.9% (n=8) of patients in Groups I, II, and III, respectively, and 5.5% (n=3), and at Month 12 in 10.5% (n=11), 8.6% (n=10), and 5.5% (n=3) of patients in Groups I, II, and III, respectively.

7.1.5. Exploratory efficacy results

7.1.5.1. Evaluation of CNV (change from Baseline to Month 12)

- *CNV leakage:* While the large majority of patients presented with CNV leakage in the study eye at Baseline (Group I, 96.2%, 101/105; Group II, 93.1%, 108/116; Group III, 100%, 55/55), in most patients in all treatment groups (FAS/LOCF) no CNV leakage was reported at Month 12 (Group I, 68.6%, n=72; Group II, 69.8%, n=81; Group III, 65.5%, n=36).
- *Area of lesion:* The area of the lesion decreased in the ranibizumab groups from Baseline to Month 12 with mean changes (SD) of -0.310 (± 1.6525) mm^2 in Group I and -0.568 (±1.9442) mm^2 in Group II. In patients in Group III, the mean area of the lesion increased from Baseline to Month 12 by 0.279 (±2.9593) mm^2.
- *Area of CNV:* The area of CNV decreased in all treatment groups from Baseline to Month 12 with mean (SD) changes of -0.248 (±1.8797) mm^2 in Group I, -0.979 (±1.6537) mm^2 in Group II, and -1.268 (±2.0413) mm^2 in Group III.
- *Greatest linear dimension:* The greatest linear dimension of the entire CNV lesion at Month 12 was on average reduced by -96.2 (±712.64) µm in Group I, -255.9 (863.36) µm in Group II, and -33.3 (965.23) µm in Group III.

7.1.5.2. Patient reported outcomes

- *NEI-VFQ-25:* This assessment instrument was assessed at Baseline, Month 3, Month 6 and Month 12. There was no information in the submission indicating that this instrument has been validated in patients with CNV due to PM.

  At Month 3, improvement in the mean composite score from Baseline was greater in patients who were randomised to ranibizumab (Group I, 5.3 points; Group II, 4.3 points) than in patients randomised to vPDT (0.3 points). For Groups I and II, changes were sustained at Month 6 (6.3 and 5.1 points, respectively), while patients randomised to Group III had a gain of 2.3 points after start of treatment with ranibizumab. By Month 12, patients in the original treatment groups maintained improvements (Group I, 6.6 points; Group II, 5.1 points), while Group III improved by 4.9 points.

Improvements in mean scores (p-values <0.05) were observed in the ranibizumab treatment groups compared with vPDT from Baseline to Month 3 in the subscales of general vision (Group I, 8.6; Group II, 7.3; Group III, -1.4), near activities (Group I, 11.5; Group II, 5.3; Group III, 0.9), mental health (Group I, 7.4; Group II, 4.9; Group III -1.8), and dependency (Group I, 3.7; Group II, 3.1; Group III, -4.7). At Months 6 and 12, these subscales maintained or slightly improved on the results observed at Month 3, and the results were generally consistent across the 2 ranibizumab groups.

Group III demonstrated improvements in NEI-VFQ-25 composite and several subscale scores after receiving ranibizumab at Month 3. Composite scores improved, on average, from 1.1 points at Month 3 to 2.3 points at Month 6, and to 4.9 points at Month 12. While there was improvement in Group III at 6 and 12 Months, results did not reach the level of change observed in Groups I and II.

- *EQ-5D:* This assessment instrument was assessed at Baseline, Month 3, Month 6 and Month 12. There was no information in the submission indicating that this instrument has been validated in patients with CNV due to PM. Furthermore, there are no vision-specific questions in the instrument, which probably accounts for the inability of the instrument to detect meaningful changes between ranibizumab and vPDT in the proposed patient population. At Month 3, more patients in Groups I and II (71% and 65%) improved on the anxiety/depression scale from 'moderately anxious' to 'not anxious' compared with Group III (51%). In the categories mobility, self-care, usual activities, and pain/discomfort there were no differences observed from Baseline to Month 3 for the ranibizumab and the vPDT treatment groups. The majority of patients (over 80%) reported 'no problems' in any category at each time point. These results were maintained for Months 6 and 12. The EQ-5D visual analogue scale reflected little to no change from Baseline to Month 3 in the ranibizumab or vPDT treatment groups and this was maintained through Months 6 and 12.
- *WPAI-GH:* This assessment instrument was assessed at Baseline, Month 3, Month 6 and Month 12. There was no information in the submission indicating that this instrument has been validated in patients with CNV due to PM. The results of the WPAI-GH total score showed a reduction in percentage of overall work impairment for all three treatment groups. The ranibizumab groups had the greatest reduction in mean change from Baseline total score at Month 3 with reductions in Groups I and II being -21.9% and -22.0%, respectively, compared with -10.2% in Group III. The sponsor stated that a 20% reduction in work productivity impairment can be interpreted as equivalent to the productivity lost by many patients with health problems, thereby suggesting productivity may have been regained for Groups I and II. Results were consistent for Groups I and II for Month 6 (-21.4% and -23.8%, respectively). However at Month 12, Group I reported a change of -0.3%, which indicates little change from baseline level of work productivity impairment, while the changes in Groups II and III were -25.0% and -19.7%, respectively. The remaining work subscales of attendance, productivity, and activity impairment demonstrated minor improvements across the three treatment groups up to Month 12.

7.1.6. Subgroup analysis of the primary efficacy endpoint

In order to further evaluate the internal consistency of the efficacy results within the FAS, pre-specified subgroup analyses across different patient categories were conducted for the primary efficacy variable. The following subgroups were evaluated: age (<45, 45 to <55, 55 to <65, ≥65 years), sex (male, female), race (Caucasian, Asian, Other), race (Japanese, non-Japanese), baseline BCVA (<45, 45 to <60, 60 to <73, ≥73 letters), baseline axial length (<28 mm, 28 to <30 mm, ≥30 mm), and baseline location of CNV subtype (subfoveal, juxtafoveal, extrafoveal, margin of the optic disc). In addition, subfoveal versus all other non-subfoveal CNV was analysed . All subgroup analyses were performed on the FAS using modified/LOCF and observed values. The mean change from Baseline in BCVA of the study eye to Month 1 through Month 3 for the subgroup analyses (FAS/modified LOCF) were summarised.

The mean changes from baseline in BCVA in the study eye at Month 6 and Month 12 for the subgroup analyses in the ranibizumab groups (Groups I and II) were also undertaken. The results for the Month 6 analysis (not shown in this CER) were examined and were generally consistent with those for Month 12.

> Comment: In all specified subgroups, a vision gain in the two ranibizumab groups compared with the vPDT group was observed with respect to the mean average change in BCVA of the study eye from Baseline to Month 1 through Month 3. The results for the subgroup analyses were similar to the primary analysis. Patients with a lower baseline BCVA score generally achieved, on average, a higher gain in BCVA from baseline. In general, there was notable inter-subject variability in the BCVA results in each of the subgroups (see SD), which most likely reflects the small sample sizes. The mean changes from baseline in BCVA in the study eye at Month 6 and Month 12 in the ranibizumab groups (Group I and II) showed that the clinically meaningful improvement in mean average change in BCVA from baseline to Month 1 through Month 3 could be maintained through Month 12.

7.1.7. Number of ranibizumab injections over the duration of the study

The submitted data included a post hoc analysis of the efficacy data in the FAS relating to the number of injections received over the duration of the study (that is, Data supporting posology recommendation, CTD 2.7.3, Summary of Clinical Efficacy, Section 4.2.1). The CSR also included a subgroup analysis of the mean number of ranibizumab injections received over the duration of the study.

7.1.7.1. Number of ranibizumab injections in Groups I and II

In Group I, treatment with 0.5 mg ranibizumab was initiated on Day 1 followed by a second mandatory treatment 1 month later (Month 1), after which re-treatment could be continued at monthly intervals until BCVA stabilization criteria were met.

In Group II, treatment with 0.5 mg ranibizumab was initiated on Day 1 and visual impairment due to disease activity was then evaluated at Month 1. If the patient exhibited disease activity, then re-treatment at monthly intervals was permitted until no further disease activity was seen.

In Group 1, the mean (SD) number of ranibizumab injections received up to Month 3 was 2.5 (0.56) compared with 1.8 (0.82) in Group II (FAS). Therefore, at Month 3 there was, on average, 0.7 fewer injections in Group II compared with Group I, while the mean change in BCVA from Baseline through to Month 3 (FAS modified LOCF) was similar in both groups (Group I, 10.5 letters and Group II, 10.6 letters). The pattern of lower mean injections in Group II compared with Group I observed from baseline up to Month 3 (1.8 versus 2.5) was maintained throughout the study with respective numbers being 2.5 versus 3.5 from baseline up to Month 6 and 3.5 versus 4.6 from baseline up to Month 12.

However, despite the smaller mean number of injections in Group II compared with Group I up to Month 6 the treatment benefit (key secondary efficacy endpoint) did not significantly differ between the two groups with the mean average increase from Baseline in BCVA being 11.7 and 11.9 letters in Groups II and I, respectively. The number of ranibizumab injections in Groups I and II in the subgroup analyses over the course of the study were consistent with the results in the overall population.

7.1.7.2. Actual treatment interruptions in Groups I and II

Response to treatment was monitored according to predefined criteria (stability in Group I, disease activity in Group II). Once these criteria were achieved, the protocol allowed for the investigator to stop/interrupt treatment. Treatment was to be restarted if the pre-specified criteria of BCVA stability were not met and/or disease activity was noted.

The percentage of patients who actually interrupted treatment at least once during the 12 month study period was 98.1% (103/105) in Group I and 95.7% (111/116) in Group II. The number of treatment free intervals is summarised below in Table 4.

Of the patients with an actual treatment interruption, the percentage who had an interruption after the minimal number of injections required by protocol (that is, at the first available time-point) was 47.6% (49/103) in Group I at Month 2 (that is, after 2 injections), and 52.3% (58/111) in Group II at Month 1 (that is, after a single injection).

The percentage of patients who were treated only with the initial injection regimen was 22.9% (24/105) in Group I (that is, 2 injections) and 29.3% (34/116) in Group II (that is, 1 injection). At the time of the actual treatment interruption (Month 2 and Month 1 for patients in Groups I and II, respectively), the mean change in BCVA was +10.0 and +9.2 letters, respectively. At Month 12, the change in BCVA was +13.6 and +12.9 letters for Group I and Group II, respectively.

Table 4. CRFB002F301 – Number (%) of patients by number of ranibizumab treatment-free intervals up to Month 11; FAS/observed.

Parameter	Ranibizumab 0.5 mg Group I by stabilization N = 105 n (%)	Ranibizumab 0.5 mg Group II by disease activity N = 116 n (%)
Number of treatment-free intervals		
0	2 (1.9)	5 (4.3)
1	55 (52.4)	64 (55.2)
2	37 (35.2)	30 (25.9)
3	10 (9.5)	11 (9.5)
4	1 (1.0)	6 (5.2)
nmiss	0	0

In Group I, 98.1% (101/103) of patients had a first-treatment interruption starting on or after Month 2 due to 'no treatment due to BCVA stability' as per-protocol defined criteria, and in Group II, 99.1% (110/111) of patients had a first-treatment interruption staring on or after Month1 due to 'no disease activity' as per-protocol defined criteria. The characteristics of the second treatment-free interval up to Month 11 were similar to the first-treatment free interval.

7.1.7.3. Duration of treatment-free intervals in Groups I and II

In Group I, for 20.4% (21/103) of patients with treatment-free intervals the duration was 10 months, which was the maximum duration possible for Group I in the 12 month period. In Group II, for 28.8% (32/111) of patients with treatment-free intervals the duration was 11 months, which was the maximum duration possible for Group II in the 12 month period. The duration of the first treatment-free interval is summarised below in Table 5.

Table 5. CRFB002F301 – Number (%) of patients by duration of first treatment-free interval up to Month 11; FAS/observed.

Duration of treatment-free interval	Ranibizumab 0.5 mg Group I by stabilization	Ranibizumab 0.5 mg Group II by disease activity
	n (%)	
Total	103	111
1 month	19 (18.4)	19 (17.1)
2 months	15 (14.6)	17 (15.3)
3 months	9 (8.7)	7 (6.3)
4 months	5 (4.9)	3 (2.7)
5 months	9 (8.7)	5 (4.5)
6 months	7 (6.8)	2 (1.8)
7 months	3 (2.9)	4 (3.6)
8 months	6 (5.8)	2 (1.8)
9 months	9 (8.7)	8 (7.2)
10 months	21 (20.4)	12 (10.8)
11 months	0	32 (28.8)

FAS = full analysis set.

- Missing visits are included in the calculation of the duration of treatment-free intervals. The end of study visit is not included in any calculation.
- First visit of a treatment-free interval must be an attended visit, following a treatment visit.

The mean change from Baseline up to Month 12 in VA varied little when analysed by different durations of treatment-free intervals (14.1 to 15.7 letters for Group I, and 13.7 to 14.8 letters for Group II).

7.1.7.4. Re-initiation of treatment in Groups I and II

To justify interruption of treatment, it needs to be shown that there is a relevant BCVA response when and if treatment is re-initiated. The following evaluations were performed for the first re-initiation treatments only. Re-initiation of treatment (treatment administered after a visit without treatment) occurred in 55.3% (57/103) of patients who interrupted treatment in Group I for the period up to Month 11 and 46.9% (52/111) of patients in Group II. From their maximum BCVA value before re-initiation of treatment, to the time-point of re-initiation, patients had lost an average of 4.6 letters and 2.5 letters in Groups I and II, respectively. The response to re-initiation of treatment was similar in both ranibizumab groups (Group I: +3.0 letters, Group II: +2.8 letters) (see Table 6, below). The average BCVA gains were of a similar magnitude as the BCVA losses prior to the re-initiation of treatment. The mean number of consecutive injections during the first re-initiation of treatment up to Month 11 was 2.1 and 1.5 in Groups I and II, respectively.

Table 6. Summary statistics of the 1-month BCVA (letters) response to the first re-initiation of treatment up to Month 11 by prior change in VA; FAS/observed.

Parameter	Statistic	Ranibizumab 0.5 mg Group I by stabilization N=57	Ranibizumab 0.5 mg Group II by disease activity N=52
At treatment	n	57	51
	Mean (SD)	63.1 (12.60)	63.3 (13.50)
	SE	1.67	1.89
	Median	63.0	67.0
	Min - Max	21.0 – 92.0	33.0 – 85.0
	1st - 3rd quartile	56.0 – 70.0	48.0 – 75.0
At 1 month post-treatment	n	57	51
	Mean (SD)	66.1 (12.71)	66.1 (12.49)
	SE	1.68	1.75
	Median	67.0	69.0
	Min - Max	34.0 – 89.0	34.0 – 86.0
	1st - 3rd quartile	57.0 – 75.0	57.0 – 76.0
Change from treatment to 1 month post-treatment	n	57	51
	Mean (SD)	3.0 (6.19)	2.8 (6.47)
	SE	0.82	0.91
	Median	2.0	3.0
	Min - Max	-7.0 - 22.0	-20.0 – 21.0
	1st - 3rd quartile	-1.0 – 6.0	0.0 – 6.0

BCVA = best-corrected visual acuity; FAS = full analysis set; VA = visual acuity.

- Visits with first treatment re-initiation up to Month 11 are included.
- N is the number of visits with treatment re-initiation.
- n is the number of re-initiations within the category where the patient was evaluable for the change in VA.

7.2. Other efficacy study – CRFB002AGB10 (REPAIR), exploratory study

7.2.1. Study design, objectives, locations and dates

Study CRFB002AGB10 (REPAIR) was not part of the sponsor's global development plan for Lucentis for the treatment of CNV secondary to PM, but was included in the submission at the request of the TGA. The Clinical Overview (CTD 2.5) indicates that this study was exploratory.

REPAIR was a Phase II, single-country (UK), multicentre (12 centres), open-label study, of 12 months duration designed to evaluate the efficacy and safety of ranibizumab (0.5 mg) in patients with choroidal neovascularization (CNV) secondary to pathological myopia (PM). The first patient was enrolled on 15 January 2010 and the last patient completed the study on 20 April 2012. The study complied with all ethical requirements.

The **primary objective** was to evaluate the mean change in best-corrected visual acuity (BCVA) from baseline to Month 12 in patients with CNV secondary to PM who were treated with ranibizumab 0.5 mg.

The **key secondary objectives** were to evaluate: (i) mean change in BCVA from baseline to Month 6; (ii) mean change in retinal thickness from baseline to Months 6 and 12; (iii) time to the first re-treatment and the total number of treatments; (iv) change in lesion size and morphology from screening to Months 6 and 12; and (v) safety of intravitreal injections of ranibizumab.

An **exploratory objective** was to evaluate the effects of ranibizumab on patient-reported outcomes from baseline to Month 12, assessed by the Macular Disease Treatment Satisfaction Questionnaire (MacTSQ) and the Well-Being Questionnaire (W-BQ12).

The **investigational plan** included a screening period of 11 days (Days -14 to -3) designed to assess enrolment eligibility. At baseline/Visit 2 (Day 0) eligible patients were assigned to treatment and received the first IVT injection of ranibizumab 0.5 mg. All patients were treated with an initial dose of ranibizumab 0.5 mg, followed by repeated monthly administration as needed for up to a further 11 months. Visits to assess efficacy and safety were scheduled at 1-

month intervals during the treatment period. Patients were contacted by the site personnel 2 days (± 1 day) after each study treatment (as required) to assess vision, local AEs and compliance with self- administration of post-injection antimicrobial medication. The primary objective was assessed at each study visit and at the end of the treatment period (Month 12).

> Comment: This Phase II study was open-label, and single-arm in design. Consequently, the study is subject to the well-known biases associated with non-randomised, non-controlled, unmasked clinical trials.

7.2.1.1. Inclusion and exclusion criteria

Male and female patients aged 18 years or older with active primary or recurrent subfoveal or juxtafoveal CNV secondary to PM were treated on an outpatient basis. The inclusion criteria are summarised immediately below and patients were required to fulfil all criteria:

- Written informed consent must be obtained before any assessment is performed.
- Male or female outpatients of any race, aged 18 years or older.
- Diagnosis of active primary or recurrent subfoveal or juxtafoveal CNV secondary to PM.
- Diagnosis of high myopia of at least -6 dioptres in the study eye spherical equivalent. For subjects who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye must have been at least -6 dioptres.
- Patients who have a BCVA score between 78 and 24 letters in the study eye using Early Treatment Diabetic Retinopathy Study (ETDRS)-like grading charts (approximately 6/9 to 6/96 Snellen equivalent).
- Patients willing and able to comply with all study procedures.

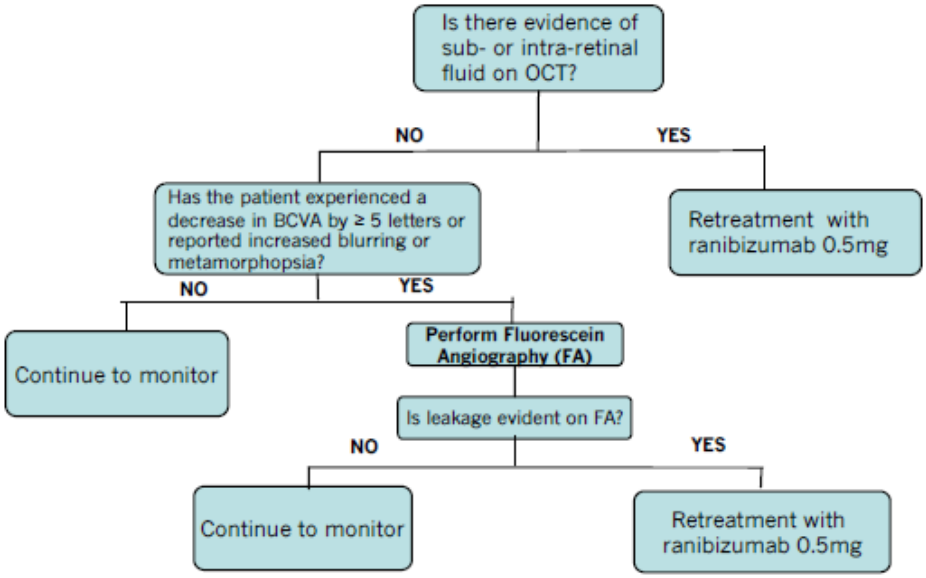
The extensive exclusion criteria have been examined and are considered to be acceptable for a study of this type.

> Comment: The inclusion and inclusion are considered to be satisfactory for a Phase II study. However, the inclusion criteria in this study did not require the detailed criteria required in the pivotal Phase III study. The exclusion criteria for the study were extensive and are considered to be consistent with those for the pivotal Phase III study.

7.2.1.2. Treatment

All patients were to be treated (study eye) with ranibizumab 0.5 mg over 12 months. The ranibizumab dose of 0.5 mg (in 0.05 ml solution) was administered initially at baseline (Visit 2), then from Month 1 (Visit 3) through Month 11 (Visit 13) as needed, but no more frequently than every 28 days. The re-treatment criteria are outlined below in Figure 2.

Figure 2. CRFB002AGB10 – Re-treatment criteria.



Study treatment was to be discontinued and the patient withdrawn from the study under the following circumstances: withdrawal of informed consent; failure to return for visits; lost to follow-up; pregnancy; use of prohibited treatments; or any other protocol deviation that resulted in a significant risk to the patient's safety. Patients who withdrew from the study prematurely were to undergo a termination visit, if possible. Patients who prematurely withdrew from the study were to be replaced by an equal number of newly enrolled patients.

Patients who successfully completed the study through Month 12/Visit 14 were considered to have completed the treatment period for the 12 month data analysis. After completion of all assessments at the final visit, the investigator continued to treat the patient according to standard clinical practice. There was no extension study.

Visudyne PDT was allowed as rescue therapy at the investigator's discretion if all of the following criteria were met: (i) there had been at least two consecutive monthly injections of ranibizumab in the immediately preceding two visits; (ii) there had been no improvement in VA or metamorphopsia; and (iii) there was leakage on fluorescein angiography. Following the use of rescue medication patients were encouraged to remain in the study and were eligible to receive further ranibizumab injections as per the re-treatment criteria. Patients were permitted to receive further rescue medication throughout the study period, although the frequency of vPDT treatment was limited to once every three months.

The study allowed specified concomitant treatments, but prohibited specified treatments. These treatments have been examined and are considered appropriate.

7.2.1.3. Analysis sets

The **Full Analysis set (FAS)** consisted of all patients who received at least one application of study treatment and had at least one post-baseline assessment for BCVA. Following the intent-to-treat principle, patients were analysed according to the treatment assigned. No data were excluded from the FAS analyses because of protocol deviations. The FAS included all 65 enrolled patients.

The **Per Protocol set (PPS)** consisted of all patients in the FAS who completed the treatment phase of the trial without clinically significant protocol deviations. Clinically significant protocol deviations were defined in the Statistical Analysis Plan. If deviations occurred, then the data from specific patients, visits, or evaluations could be excluded from the PPS. The criteria and determination of clinically relevant protocol deviations and patient specific identification of

data to be excluded from the PPS were finalised prior to database lock. The PPS included 60 (92.3%) of the 65 enrolled patients.

The **Safety set** consisted of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment. Patients were analysed according to treatment received. The safety set include all 65 enrolled patients.

7.2.1.4. Primary efficacy variable – definition, statistical analysis and sample size

The primary efficacy variable was the difference from baseline to Month 12 in the level of BCVA (letters) in patients treated with ranibizumab. The sponsor stated that 'although the present study was non-comparative, if it could be demonstrated that ranibizumab improved vision at 12 months then this would provide the first substantive evidence for the efficacy of ranibizumab in CNV secondary to PM. A clinically important improvement in VA is considered to be 10 letters'.

The **null hypothesis** was:

H0: $\theta = 0$ versus H1: $\theta \neq 0$; where θ was the mean change from baseline to 12 months in BCVA.

The null hypothesis was tested by a paired t-test. The mean change from baseline to 12 months in BCVA was presented together with 95% confidence interval. The primary analysis was performed on the FAS using the LOCF method to impute missing data. In the event that a subject received rescue medication and continued in the study, the last observed value prior to receipt of rescue medication was used in the LOCF procedure.

For **sensitivity purposes**, the primary analysis was repeated using the PPS. For the PPS, it was assumed that a complete set of valid observations for the efficacy endpoints would be available. Therefore, no general rules for handling of missing values were specified.

For the primary efficacy variable (change in BCVA from baseline to 12 months), **a sample size** of 58 was estimated to have 90% power to detect a difference in mean BCVA of 10, assuming a standard deviation of differences of 23, using a paired t-test with a 0.05 two-sided significance level.

An **interim analysis** was performed when 75% of patients (n=48) had been followed up for six months, to provide data on the short-term efficacy/safety benefit of ranibizumab treatment in CNV due to PM, increase the experience with guided individualized ranibizumab treatment on an ongoing basis and allow a decision to be made whether to continue the study. Results of the interim analysis did not show any evidence of a mean deterioration in VA or safety concerns, and did not result in early termination of the study. As the study was open-label with a single treatment group and the primary efficacy variable was not to be examined at the time of the interim analysis, no adjustments for multiple testing were required.

7.2.1.5. Other efficacy variables – definition and statistical analysis

(a) Secondary efficacy variables

- Mean change in BCVA from baseline to Month 6, percentage of patients gaining ≥ 15 letters, and percentage of patients losing ≥ 15 letters. BCVA was assessed in a sitting position using ETDRS-like VA testing charts at an initial distance of 4 metres moving to 1 metre if the total number of letters read was ≤ 3. A Total Visual Acuity score was recorded for each eye. If this score was 0 at 1 metre, the Count Fingers test was to be performed, and the maximum distance recorded in the CRF. If Count Fingers was not measurable, then the Hand Motion test was to be performed. If Hand Motion was not measurable, then the Light Perception test was to be performed.
- Mean change in CRT in µm from baseline to Months 6 and 12, and presence or absence of intraretinal cysts and subretinal fluid. These parameters were assessed by OCT.
- Mean change in lesion area (mm^2) from screening (pre-treatment) to Months 6 and 12, change in fluorescein leakage from screening (pre-treatment) to Months 6 and 12, and

presence or absence of subretinal/intraretinal hemorrhage or any other disease. These parameters were assessed using colour fundus photography and fluorescein angiography:

- The analysis of the secondary efficacy objectives focused on the FAS. Hypothesis tests carried out at time-points other than 6 and 12 months were considered to be exploratory.

(b) Exploratory patient reported outcomes

Patient reported outcomes were assessed by the 12-item well-being questionnaire (W-BQ12), and the macula disease treatment satisfaction questionnaire (MacTSQ). Descriptive statistics for changes from baseline to Months 6 and 12 were presented for both questionnaires.

7.2.1.6. Participant flow protocol violations

In total, 84 patients were screened. Of these, 19 did not fulfil entry criteria and were not enrolled. The most frequent reasons for non-enrollment were: not meeting diagnostic/severity criteria (n=7); unacceptable test procedure result (n=3); and unacceptable past medical history/concomitant diagnosis (n=2). Of the 65 patients enrolled in the study, 62 (95.4%) completed and 3 (4.6%) discontinued. The primary reasons for discontinuation were unsatisfactory therapeutic effect (1 patient, 1.5%), protocol violation (1 patient, 1.5%) and lost to follow-up (1 patient, 1.5%).

All 65 patients had at least one protocol deviation. Non-compliance with the VA masking procedures (presumably procedures for masking the previous visit VA results) were reported in all 65 patients. Other frequent protocol deviations were missing a secondary efficacy assessment (n=21), and missing area of lesion assessment (n=18) at Visits 1, 3, 6 or 12, and missing telephone contact entirely or within five days after treatment (n=15). Six patients missed a study visit, and 6 patients received a prohibited treatment (NSAID therapy for all 6 patients). One patient also received warfarin continuously throughout the study. One protocol deviation (malignancy diagnosed within five years of study entry) resulted in discontinuation.

7.2.1.7. Baseline data

The mean (SD) age of the 65 enrolled patients was 55.5 (14.97) years, ranging from 21 to 92 years. The age (years) distribution of the 65 enrolled patients was < 50 (21, 32.3%), 50 to < 65 (29, 44.6%), 65 to < 75 (10, 15.4%), 75 to < 85 (3, 4.6%), and ≥ 85 (2, 3.1%). The enrolled population was predominantly female (46, 70.8%). The majority of enrolled patients were Caucasian (59, 90.8%) with the remainder being Black (1, 1.5%), Oriental (2, 3.1%) or Other (3, 4.6%). The mean (SD) height and weight of the 64 enrolled patients with data were 165.6 (10.13) cm and 76.79 (17.998) kg, respectively.

All 65 enrolled patients had diagnoses of CNV and PM. The mean (SD) duration of CNV prior to study entry in 65 patients with data was 1.78 (3.259) months, with a range of 0 to 18.6 months. The mean (SD) duration of PM prior to study entry in 58 patients with data was 39.89 (20.520) years, with a range of 0.3 to 84.1 years. The right eye was the study eye in 55.4% of cases. The mean (SD) BCVA score in the study eye at baseline was 59.5 (13.59) letters, with a range of from 26 to 85 letters. The distribution of BCVA (letters) in the enrolled patients was 23-37 (4, 6.2%), 28-52 (16, 24.6%), 53-67 (25, 38.5%), 68-82 (19, 29.2%), and > 82 (1, 1.5%).

The mean (CRT) in 62 enrolled patients with data was 384.7 (130.99) µm, with a range of 107 to 812 µm. Intraretinal oedema with centre involvement was present in 57 (87.7%) patients and absent in 8 (12.3%) patients. Intraretinal cysts were definitely present in 34 (52.3%) patients, absent in 21 (32.3%) patients and questionable in 10 (15.4%) patients. Subretinal fluid was definitely present in 44 (67.7%) patients, absent in 17 (26.3%) patients, and questionable in 4 (6.2%) patients.

The CNV location was subfoveal in 43 (66.2%) patients, juxtafoveal in 17 (26.2%) patients, and probably subfoveal/juxtafoveal in 5 (7.7%) patients. The mean (SD) area of the lesion in the 65 enrolled patients was 1.463 (1.3511) mm^2, with a range of 0.12 to 6.56 mm^2, and

subretinal/intraretinal haemorrhage was present in 41 (63.1%) and absent in 24 (36.9%) patients.

Standard ophthalmoscopy examinations at baseline showed clinically significant abnormalities of the retina in 6 (9.2%) patients, and of the choroid in 5 (7.7%) patients. Clinically significant abnormalities of the macula were observed in 61 (93.8%) patients. Inflammation of the study eye was rare, with inflammation of the anterior chamber cells, the conjunctiva and vitreous cells occurring in 1 patient each. Previous eye disorders in the study eye other than CNV and myopia included cataract in 4 (6.2%) patients and diabetic retinopathy in 2 (3.1%) patients. No other eye disorders affected more than 1 patient. CNV in the fellow was reported in 6 (9.2%) patients. Prior to study entry, 9 (13.8%) patients had undergone a surgical or medical procedure on the study eye, including 5 (7.7%) patients with a previous cataract operation, and 7 (10.8%) patients had undergone a surgical or medical procedure on the fellow eye.

7.2.2. Results for the primary efficacy variable

In FAS/LOCF analysis (n=65), the mean (SD) baseline BCVA was 59.5 (13.58) letters, ranging from 26 to 85 letters, and the mean (SD) BCVA at Month 12 was 73.1 (13.13) letters, ranging from 27 to 94 letters. For the primary efficacy variable of difference in BCVA from baseline to Month 12, the estimated mean (SD) difference was 13.60 (13.862) letters (95% CI: 10.17, 17.03), p< 0.001, and the mean difference ranged from -19.0 to 49.0 letters. The two-sided 95% CI was derived from a t-distribution, and the p-value was derived from a paired t-test. The median increase from baseline to Month 12 was 10 letters, and the baseline and Month 12 medians were 60.0 and 75.0 letters, respectively.

The mean increase in BCVA from baseline exceeded 10.00 letters at all monthly visits through to Month 12, apart from Months 1, 3, and 5. Of note, the mean increase in BCVA remained above 10.00 letters at each monthly visit from Month 6 to Month 12, inclusive. The mean improvement from baseline in BCVA ranged from 8.71 to 14.15 letters throughout the study. In the fellow eye, the mean (SD) difference in BCVA from baseline to Month 12 was 2.95 (12.048) letters, and was in the range -0.54 to 2.95 letters throughout the study.

The results for the sensitivity analysis in the PPS/LOCF were consistent with the results from the primary analysis in the FAS/LOCF. In the PPS (n=60), the mean change in BCVA from baseline to study end-point was 14.10 (95% CI: 10.43, 17.77) letters; p<0.001. In the PPS, 2 patients failed to provide VA data at Month 12 and for these patients the LOCF approach was used to impute the missing data.

> Comment: The mean improvement in BCVA from baseline to Month 12 was stated by the sponsor to be 'clinically important' as it exceeded 10 letters. However, in the absence of a randomised, masked placebo-control it cannot be definitively concluded that the observed improvement is 'clinically important'. The variability in the estimated mean difference from baseline to month 12 was highly variable as can be seen from both the SD of the mean and the range of the estimated mean difference.

7.2.3. Results for the secondary efficacy variables

1. **Change in BCVA:** During the period from baseline to Month 12, 24 (36.9%) patients achieved a BCVA gain of ≥ 15 letters in the study eye, and 33 (50.8%) patients achieved a gain of ≥ 10 letters. Only one patient (1.5%) reported a loss of ≥ 15 letters in the study eye. No subject had a BCVA level below 0 for the study eye at any visit. In contrast to the study eye, only 5 (7.7%) and 7 (10.8%) of patients reported a gain of ≥15 letters or ≥10 letters in the fellow eye, respectively, during the 12 month study period. The proportion of patients reporting that the study eye was better than the fellow eye increased from 26.2% (n=17) at baseline to 34.4% (n=22) at Month 12, while the proportion of patients describing the study eye as worse than the fellow eye decreased from 73.8% (n=48) to 59.4% (n=38).
2. **Change in lesion area:** Fluorescein angiography and fundus photography showed that there was a significant reduction in the lesion area in the study eye from baseline to Month

6 and to Month 12. Based on patients in whom evaluable measurements were available at baseline and at Month 6 (n=48), the mean (SD) change in lesion was -0.51 (0.994) mm^2, p=0.0008. For patients with evaluable measurements at baseline and Month 12 (n=50), the mean (SD) change was -0.37 (1.161) mm^2, p=0.0287.

3. **Leakage:** Month 6, data on fluorescein leakage were recorded in 55 of the 65 patients. Of these, 45 patients had a complete absence of leakage, 9 patients had leakage within the original leakage area and 1 patient had progression compared to the original leakage area. At Month 12, data were available in 59 patients, of whom 54 showed a complete absence of leakage and 4 had leakage within the original leakage area (results could not be graded in 1 patient).
4. **Subretinal/intraretinal haemorrhage:** The prevalence of subretinal/intraretinal hemorrhage was 6.5% (4/62 patients) at Month 6 and 1.6% (1/64 patients) at Month 12. These values compare favorably to the baseline incidence of 63.1% (41/65 patients).
5. **Change in CRT:** OCT data were available at baseline and Month 6 in 59 patients and at baseline and Month 12 in 61 patients. There was a significant reduction in mean (SD) CRT from baseline (387.5 [133.240] μm) to Month 6 (256.72 [82.714] μm), with a mean (SD) decrease of 128.76 (127.840) μm (p<0.001). This improvement in CRT was maintained at Month 12, when the mean (SD) reduction from baseline was 135.16 (134.117) μm (p<0.001) (that is, 386.56 [131.108] μm at baseline to 251.39 [78.060] μm at Month 12). The reduction in CRT was apparent by Month 1 and was maintained through to Month 12.
6. **Intraretinal cysts:** The proportion of patients with intraretinal cysts reduced significantly from baseline to Month 6 and to Month 12. Comparisons of proportions at 6 and 12 months were made for absent versus combined definite/questionable. At baseline, OCT results showed intraretinal cysts to be absent in 32.3% (21/65) of patients, definite in 52.3% (34/65) and questionable in 15.4% (10/65). At Month 6, these proportions had changed to absent in 80.0% (52/65), definite in 7.7% (5/65) and questionable in 4.6% (3/65), with no evaluable data in 2 patients (p<0.001). At Month 12, intraretinal cysts were absent in 83.1% (54/65) of patients, definite in 13.8% (9/65) and questionable in 1.5% (1/65) (p<0.001).
7. **Subretinal fluid:** The proportion of patients with subretinal fluid decreased from baseline to Month 6 and Month 12. Comparisons of proportions at 6 and 12 months were made for absent versus combined definite/questionable. Subretinal fluid was absent, definite or questionable in 26.2% (17/65), 67.7% (44/65) and 6.2% (4/65) of patients at baseline, and was absent, definite or not available in 81.5% (53/65), 12.3% (8/65) and 1.5% (1/65) at Month 6 (p<0.001). By Month 12, 89.2% (58/65), 7.7% (5/65) and 1.5% (1/65) of patients had absent, definite or questionable subretinal fluid on OCT (p<0.001).

7.2.4. Re-treatment

The median number of treatments during the 12 month study was 3.0, and the mean (SD) number of treatments was 3.6 (2.57). At least one re-treatment after the baseline injection was required in 51 patients (78.5%). The most frequent numbers of re-treatments were one (18.5%), two (16.9%) and three (15.4%). The most frequent cumulative numbers of injections during the 12 month study were one (21.5% of patients), two (18.5%), three (16.9%) and four (15.4%). Two patients (3.1%) received 12 injections, the maximum possible number.

Time to first re-treatment was calculated as the time difference in months starting from the date of the first treatment until the date of first re-treatment. The median time to first re-treatment following the baseline treatment was 2.00 months (95% CI 1.25, 3.42) (Kaplan-Meier estimates). The Kaplan-Meier plot suggested that all patients requiring re-treatment did so within 8 months of their baseline injection.

7.3. Evaluator's conclusions on clinical efficacy for the proposed indication

The efficacy of ranibizumab for the treatment of VA due to CNV secondary to PM is supported by one pivotal Phase III study (CRFB002F2301). The sponsor stated that this study was presented as the single confirmatory study for registration purposes. However, the TGA requested inclusion of the Phase II, open-label, single-arm study (REPAIR). The sponsor indicated that REPAIR was not part of the global clinical development program for the new indication and was not intended to be used as supportive evidence for the proposed indication.

7.3.1. Pivotal Phase III study

The pivotal Phase III study was multinational, multicentred, randomised, active-controlled, and double-masked in design and allocated patients with VA due to CNV secondary to PM to 12 months treatment with one of three treatment regimens (ranibizumab/stability, ranibizumab/disease activity and vPDT).

In Group I, patients were randomised to ranibizumab 0.5 mg and two initial injections were administered (first injection on Day 1 and second injection one month later), after which monthly injections could be continued until the BCVA stabilization criteria were met (that is, no change in BCVA as compared to two preceding visits).

In Group II, patients were randomised to ranibizumab 0.5 mg and treatment was initiated with one injection on Day 1, after which monthly injections could be continued if the disease activity criteria were met (that is, vision impairment attributable to intra- or subretinal fluid or active leakage secondary to PM as assessed by OCT and/or FA).

In Group III, patients were randomised to vPDT and received treatment at Day 1 with verteporfin 6 mg/m^2 IVI for 10 minutes, followed 15 minutes after the start of the infusion by laser SF rate of 600 mW/cm^2 for 83 seconds with light dose of 50 J/cm^2. From Month 3 through 12, the investigator could elect to treat patients in Group III with ranibizumab 0.5 mg, vPDT, or a combination of ranibizumab 0.5 mg and vPDT, if disease activity criteria were observed. Although combination vPDT/ranibizumab was a potential treatment option from Month 3 onwards for patients in Group III, no patients received combination treatment.

The primary efficacy variable was the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from Month 1 through Month 3 and the Baseline level of BCVA (Group I versus Group III; Group II versus Group III). Both ranibizumab treatment groups demonstrated statistically significant superior efficacy compared with vPDT for mean average change in BCVA from Baseline to Month 1 through Month 3 (FAS/modified LOCF). The mean average change in BCVA score of the study eye was 10.5 letters in Group I (n=105), 10.6 letters in Group II (n=116) and 2.2 letters in Group III (n=55). For both pairwise comparisons (that is, Group I versus Group III; Group II versus Group III), the mean average change in BCVA from Baseline to Month 1 through Month 3 was statistically significantly greater in patients treated with ranibizumab compared with patients treated with vPDT (that is, one-sided nominal $p < 0.00001$ for both pairwise comparisons; and confirmatory one-sided p-value of ≤0.001, adjusted for multiplicity, for both pairwise comparisons). The difference in the LSMs in the BCVA between ranibizumab (Group I) and vPDT (Group III) was 8.5 letters (95% CI: 5.8, 11.2), and between ranibizumab (Group II) and vPDT (Group III) was 8.6 letters (95% CI: 6.1, 11.1). The difference in BCVA in favour of ranibizumab compared with vPDT is considered to be clinically meaningful for both pairwise comparisons.

The key secondary efficacy variable in the pivotal study was the average level of BCVA over all monthly post-baseline assessments from Month 1 through Month 6 compared with the Baseline level of BCVA for the pairwise comparison between the two ranibizumab treatment groups (FAS/modified LOCF). The mean average change from Baseline to Month 1 through Month 6 in BCVA was similar in patients in Group I (ranibizumab/stabilization; n=105) and in Group II (ranibizumab/disease activity; n=116); 11.9 and 11.7 letters, respectively, nominal one-sided $p < 0.00001$. The mean average change in Group II was statistically non-inferior compared with

Group I (that is, one-sided $p < 0.025$, adjusted for multiplicity of pairwise testing of primary and key secondary efficacy endpoints). The difference in the LSMs for the BCVA between Group I and II of -0.1 letters (95% CI: -2.2, 2.0) is considered to be clinically insignificant.

The results for the other secondary efficacy endpoints in the pivotal study should be considered to be 'exploratory' because the p-values for all pairwise comparisons were nominal rather than confirmatory (that is, not adjusted for multiple pairwise testing). However, the observed outcomes for all secondary efficacy endpoints consistently supported the efficacy of treatment with ranibizumab for the proposed indication. In particular, rapid improvement in VA was observed at Month 1 in Groups I and II, with most of the improvement in VA being reached by Month 2. Clinically, meaningful improvement in BCVA in both ranibizumab groups was maintained from Month 2 through to Month 12. The mean improvements in BCVA (letters) from baseline in Groups I, II and III were, respectively, 12.1 versus 12.5 versus 1.4 at Month 3, 13.7 versus 12.7 versus 7.9 at Month 6, and 13.8 versus 14.4 versus 9.3 at Month 12. The improvement in BCVA at Months 6 and 12 compared with Month 3 in Group III is most likely to be associated with ranibizumab treatment allowed in this group after Month 3. The mean average change in BCVA from Baseline to Month 1 through Month 12 was 12.8 letters in Group I (ranibizumab/stratified[1]), 12.5 letters in Group II (ranibizumab/disease activity), and 6.4 letters in Group III (ranibizumab allowed after Month 3).

The proportion of patients (FAS, modified/LOCF) who gained ≥15 letters (or reached a BCVA of ≥84 letters) from Baseline increased continuously throughout the treatment period and was notably higher in ranibizumab treated patients compared with vPDT treated patients: 38.1% versus 43.1% versus 14.5% up to Month 3, 46.7% versus 44.8% versus 27.3% up to Month 6, and 53.3% versus 51.7% versus 32.7% up to Month 12 in Groups I, II and III, respectively. Similarly, a gain of ≥10 letters (or reached a BCVA of ≥84 letters) was seen in 61.9% versus 65.5% versus 27.3% of patients up to Month 3, in 71.4% versus 64.7% versus 45.5% of patients up to Month 6, and in 69.5% versus 69.0% versus 49.1% of patients up to Month 12 in Groups I, II, and III, respectively.

The proportion of patients (FAS, modified/LOCF) who lost ≥15 letters from Baseline was 1.9% versus 0% versus 7.3% up to Month 3, 0% versus 0.9% versus 3.6% up to Month 6, and 1.9% versus 0.9% versus 3.6% up to Month 12, in Groups I, II and III, respectively. The proportion of patients who lost ≥ 10 letters was 1.9% versus 0.9% versus 16.4% up to Month 3, 1.9% versus 2.6% versus 3.6% up to Month 6, and 4.8% versus 1.7% versus 3.6% up to Month 12, in groups 1, II, and III respectively. Overall, loss of ≥ 10 and ≥ 15 letters occurred infrequently in both Groups I and II.

The anatomical secondary efficacy endpoints all supported ranibizumab in both Groups I and II (that is, change in CRT over time, change in CFT over time, proportion of patients with subretinal fluid, proportion of patients with intraretinal oedema, and proportion of patients with intraretinal cysts). In particular, the mean reduction in CRT from Baseline to Month 3 in patients receiving ranibizumab was 61.0 µm (Group I) and 77.6 µm (Group II), while the corresponding result in patients receiving vPDT (Group III) was 12.0 µm. From Baseline to Month 6, mean reductions in CRT were 66.1 µm, 74.8 µm, and 51.5 µm for patients in Group I, II and III, respectively, and from Baseline to Month 12, mean reductions in CRT were 66.6 µm, 71.3 µm, and 60.8 µm for patients in Group I, II and III, respectively. As patients in Group III were allowed to receive treatment with ranibizumab from Month 3 onwards, the results for this treatment group at Months 6 and 12 are likely to be associated with ranibizumab treatment. The exploratory endpoints relating to evaluation of change in CNV parameters from baseline to Month 12, and change in patient reported outcomes over time all supported the efficacy of ranibizumab in both Groups I and II.

[1] Erratum: Ranibizumab/stabilization

7.3.2. Dosage recommendation based on results from the pivotal Phase III study

In the pivotal Phase III study, the efficacy of ranibizumab was similar in Group I (re-treatment based on stabilization criteria) and in Group II (re-treatment based on disease activity criteria), and was superior to vPDT (Group III). In Group 1 (FAS), the mean (SD) number of ranibizumab injections received up to Month 3 was 2.5 (0.56) compared with 1.8 (0.82) in Group II (FAS). Therefore, at Month 3, on average, patients in Group II received 0.7 fewer injections than patients in Group I, while the mean change in BCVA from Baseline through to Month 3 (FAS/modified LOCF) was similar in both groups (Group I, 10.5 letters and Group II, 10.6 letters). The pattern of fewer mean injections in Group II compared with Group I observed from Baseline up to Month 3 (1.8 versus 2.5), was also observed from Baseline up to Month 6 (2.5 versus 3.5), and from Baseline up to Month 12 (3.5 versus 4.6). In addition, the data relating to patients who interrupted treatment, duration of treatment-free intervals, and first re-initiation of treatment were comparable between Groups I and II. The key secondary efficacy endpoint compared changes in BCVA from Baseline at Month 6 in the two ranibizumab groups. This endpoint showed that treatment benefit was not inferior in Group II despite fewer injections than in Group I (mean average increase from Baseline in BCVA of 11.7 and 11.9 letters, respectively). Overall, the data support the ranibizumab treatment regimen based on disease activity criteria as, on-average, patients in Group II required one less injection than patients in Group I while efficacy in both groups were similar.

7.3.3. Exploratory Phase II study (REPAIR) – limited supportive data from

The supportive efficacy data from REPAIR (exploratory Phase II study) is considered to be limited due to the well-known biases associated with non-randomised, non-controlled, non-masked, single-arm studies. In REPAIR (n=65; FAS/LOCF), the mean (SD) baseline BCVA was 59.5 (13.58) letters, ranging from 26 to 85 letters, and the mean (SD) BCVA at Month 12 was 73.1 (13.13) letters, ranging from 27 to 94 letters. For the primary efficacy variable (difference in BCVA from baseline to Month 12), the estimated mean treatment difference was 13.60 letters (95% CI: 10.17, 17.03) with a p-value of < 0.001. The sponsor considered an improvement of 10 letters in BCVA to be clinically important, but in the absence of a placebo control it is difficult to unequivocally conclude that the improvement is clinically meaningful. The mean BCVA level increased from baseline by over 10 letters by Month 2, and this improvement was generally maintained throughout the 12 month study.

During the period from baseline to Month 12, 24 (36.9%) patients achieved a BCVA gain of ≥ 15 in the study eye, and 33 (50.8%) patients achieved a BCVA gain of ≥ 10 letters. Only one patient (1.5%) reported a loss of ≥ 15 letters in the study. No subject had a BCVA below 0 letters in the study eye at any visit. In contrast to the study eye, only 5 (7.7%) and 7 (10.8%) patients reported a gain of ≥15 letters or ≥10 letters in the fellow eye, respectively, during the 12 month study period.

In REPAIR, functional improvement in BCVA achieved with ranibizumab was consistent with anatomical improvement based on FA and FP, which demonstrated a significant reduction in the size of lesion in the study eye from baseline to Month 6 and to Month 12, a marked reduction in the proportion of patients experiencing fluorescein leakage, and cessation of subretinal/intraretinal haemorrhage by Month 12 in all but one of the 41 patients with this condition at baseline. In addition, OCT measurements demonstrated a reduction in CRT as early as Month 1, with a significant reduction at Month 6 that was maintained through to Month 12, accompanied by a reduced incidence of both intraretinal cysts and subretinal fluid.

The functional and anatomical results of treatment with ranibizumab in REPAIR were achieved with a mean (SD) 3.6 (2.57) ranibizumab injections over the 12 month treatment period, with 78.5% of patients requiring at least one re-treatment after the baseline injection and the first re-treatment taking place after a median interval of two months (Kaplan-Meier estimate). The Kaplan-Meier plot suggested that all patients requiring re-treatment did so within 8 months of the baseline injection.

7.3.4. Guidelines for submissions supported by only one pivotal study

The sponsor states that the submission for the proposed extension of indication is supported by one pivotal Phase III study only (CRFB002F2301). Consequently, it is considered appropriate to apply the 'prerequisites for one study applications' listed in the TGA adopted EMEA document (CPMP/EWP/2330/99), *Points to Consider on application with 1. Meta-analyses; 2. One pivotal study*. This document states that 'where the confirmatory evidence is provided by one pivotal study only, this study will have to exceptionally compelling' and provides criteria to which the regulatory evaluation should pay special attention (Section III.2). The criteria have been applied to the pivotal Phase III study and are considered to support the submission of one pivotal study. The pivotal Phase III study is considered to meet the following criteria: (i) internal validity; (ii) external validity; (iii) clinically relevant (the estimated size of treatment benefit [that is, improvement in BCVA from baseline] is considered to be clinically meaningful; (iv) the statistical significance of the pairwise comparisons between ranibizumab [Groups I and II] and vPDT [Group III] is robust for the primary efficacy endpoint and is considered to be 'considerably stronger than p=0.05' for both comparisons; (v) the data quality was good; (vi) the internal consistency was excellent for all efficacy endpoint analyses; (vii) the study was conducted in 276 patients at 80[2] centres but due to low patient numbers per centre the potential impact of individual centres could not be assessed; the maximum number of patients per centre was 14 and consequently the results were not dominated by one centre; and (viii) the tested hypothesis was plausible.

8. Clinical safety

8.1. Studies providing evaluable safety data

The submission included two studies providing evaluable safety data in patients with impairment of VA due to CNV secondary to PM (pivotal Phase III study CRFB002F2301; supportive Phase II study CRFB002AGB10).

The pivotal Phase III study included 277 patients in the safety set (262 treated with ranibizumab), including 106 patients treated with ranibizumab in Group I, 118 treated with ranibizumab in Group II, and 38 patients from Group III treated with ranibizumab from Month 3 to Month 12. The supportive Phase II study included 65 patients in the safety set.

In this CER, the safety of ranibizumab for the treatment of patients with impairment of VA due to CNV secondary to PM will be assessed the pivotal Phase III and the supportive Phase II studies separately.

8.2. Pivotal Phase III study CRFB002F2301

8.2.1. Patient exposure

8.2.1.1. Overall exposure in the safety sets

In this study, patients received either ranibizumab at 0.5 mg/0.05 mL and/or vPDT at 6 mg/m^2 followed by a SF rate of 600 mW/cm^2 delivered for 83 seconds with light dose of 50 J/cm^2. The safety set consisted 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 AEs also constituted a safety assessment. Patients were analysed by treatment received.

The safety set in the pivotal study included all 277 randomised patients (n=106, Group I, ranibizumab/stabilization; n=118, Group II, ranibizumab/disease activity; n=53, Group III, vPDT). In Group III, 2 patients randomised to vPDT received 1 active ranibizumab injection

[2] Erratum: 76 centres

prior to Month 3 and were reported in Group II for all safety analyses, but were excluded from the Month 3 and 6 PP sets. The safety set for the safety analyses at different periods is summarised below in Table 7.

Table 7. CRFB002F2301 – Safety analysis periods; safety set.

	Ranibizumab 0.5 mg			vPDT		
Safety analysis periods	Group I by stabilization n (%)	Group II by disease activity n (%)	Group III prior to Month 3 n (%)	Group III with 0.5 mg ranibizumab from Month 3 n (%)	Group III without 0.5 mg ranibizumab from Month 3 n (%)	Total n (%)
Total	**106 (100.0)**	**118 (100.0)**	**53 (100.0)**	**-**	**-**	**277 (100.0)**
Day 1 to Month 3	106 (100.0)	118 (100.0)	53 (100.0)	-	-	277 (100.0)
Day 1 to Month 6	106 (100.0)	118 (100.0)	-	34 (100.0)	19 (100.0)	277 (100.0)
Day 1 to Month 12	106 (100.0)	118 (100.0)	-	38 (100.0)	15 (100.0)	277 (100.0)
Month 3 to Month 6	103 (97.2)	118 (100.0)	-	34 (100.0)	19 (100.0)	274 (98.9)
Month 3 to Month 12	103 (97.2)	118 (100.0)	-	38 (100.0)	15 (100.0)	274 (98.9)

Percentages are based on the total number of patients in the Safety set.

8.2.1.2. Number of injections (safety-set data)

The mean number of ranibizumab injections up to Month 3 was 0.7 higher in patients treated according to stabilization criteria (Group I: mean±SD, 2.5±0.57; range 1-3) than in patients treated according to disease activity criteria (Group II: mean±SD, 1.8±0.82; range 1-3). Up to Month 3, similar proportions of patients in Group I received either 2 or 3 injections (47.2% and 49.1%, respectively), and 4 (3.8%) patients were given a single treatment only. In Group II, up to Month 3 patients most frequently received a single injection (44.9%), while a similar proportion of patients received either 2 or 3 injections (29.7% and 25.4%, respectively).

The mean±SD number of ranibizumab injections up to Month 6 was higher in patients treated according to stabilization criteria (Group I: 3.5±1.46; range 1-6) than in patients treated according to disease activity criteria (Group II; 2.5±1.56; range 1-6). Up to Month 12, the mean±SD number of ranibizumab injections was higher in patients treated according to disease stabilization criteria (Group I 4.6±2.59; range: 1-11) than in patients treated according to disease activity criteria (Group II: 3.5±2.92; range 1-12). Overall, there was approximately 1 additional injection required in both Groups I and II during the second 6 months of the study, compared with the first 6 months of the study. Up to Month 12, 58.5% (62/106) of patients in Group I received 1-4 injections, and 50.0% (59/118) of patients in Group II received 1-2 injections.

In Group III (vPDT), of the 53 patients in the safety set 38 (71.7%) patients were treated with ranibizumab from Month 3 though Month 12. The majority of patients who received ranibizumab were treated with 1 or 2 injections. The mean number of ranibizumab injections in Group III was 1.9 injections up to Month 6, and 3.2 injections up to Month 12. There were 15 patients in Group III group who did not receive any ranibizumab injections during the study. No patients in Group III received both vPDT and ranibizumab from Month 3 through Month 12.

8.2.1.3. Proportion of patients treated by visit (safety-set data)

The proportion of patients in Groups I and II re-treated with ranibizumab from Month 1 through Month 12 in the safety set is summarised below in Table 8. The percentages are based on the total number of patients still in the study at the specific visit that did not miss the visit, and represent all patients re-treated with ranibizumab irrespective of assessment and treatment recommendation. The results show that the percentage of patients in each group requiring re-treatment at each visit from Month 1 through Month 6 was generally lower than from Month 7 through Month 11.

Table 8. CRFB002F2301 – Proportion of patients in Groups I and II retreated with ranibizumab from Month 1 through Month 12, irrespective of assessment and treatment recommendation; safety set.

Month	Group I Proportion Retreated		Group II Proportion Retreated	
1	97.1%	102/105	47.5%	56/118
2	50.0%	52/104	36.4%	43/118
3	26.1%	30/115	36.9%	38/103
4	32.7%	33/101	23.7%	28/118
5	30.1%	31/103	17.8%	21/118
6	23.8%	24/101	20.5%	24/117
7	25.0%	25/100	17.2%	20/116
8	22.2%	22/99	17.0%	19/112
9	17.0%	17/100	20.7%	23/111
10	21.6%	21/97	12.5%	14/112
11	13.7%	13/95	13.4%	15/112

In Group I, the proportion of patients re-treated with ranibizumab at Month 1 (re-treatment specified in the protocol for all patients) was 97.1% (102/105), and at Months 2, 5, 8, and 11 the proportion of patients re-treated with ranibizumab based on assessment of lack of stability (irrespective of disease activity) was 50.0% (52/104), 29.1% (30/103), 22.1% (22/99), and 13.7% (13/95), respectively. In Group II, the proportion of patients re-treated with ranibizumab based on assessment of disease activity (irrespective of stability) at Months 1, 2, 5, 8, and 11was 45.8% (54/118), 34.7% (41/118), 16.9% (20/118), 17.0% (19/112), and 13.4% (15/112), respectively.

8.3. Adverse events

8.3.1. Overview

AEs were deemed treatment emergent if the date of onset was on or after the date of first study treatment. Treatment-emergent AEs, deaths, SAEs, and AEs leading to discontinuation of study treatment were listed separately and summarised by primary SOC and preferred term.

The safety data were summarised for three different time periods:

- Up to Month 3 – The safety for the two ranibizumab treatment groups (Group I, ranibizumab re-treatment driven by stability criteria; Group II, ranibizumab re-treatment driven by disease activity criteria) were compared with vPDT (Group III).
- Up to Month 6 – The safety data up to Month 6 were assessed for the two ranibizumab treatment groups (Groups I and II); and the safety data from Month 3 to Month 6 were assessed for Group III with and without ranibizumab.
- Up to Month 12 – The safety data up to Month 12 were assessed for the two ranibizumab treatment groups (Groups I and II); and the safety data from Month 3 to Month 12 were assessed for Group III with and without ranibizumab.

The number and percentage of patients who reported AEs identified as safety concerns (based on selected preferred terms) in the current version of the Lucentis Risk Management Plan (RMP) at the time of the Month 6 and the Month 12 database locks, were summarised by risk categories for ocular (study/fellow eye) and systemic concerns. For these AEs, the 95% CI for the proportion of patients experiencing the events were presented using the Clopper Pearson exact method, and for the up to Month 3 analyses, relative risk ratios describing the differences between the ranibizumab groups and the vPDT group were calculated.

8.3.2. Ocular AEs

8.3.2.1. Ocular AEs occurring regardless of relationship to treatment

8.3.2.1.1. Commonly occurring ocular AEs

(a) Up to Month 3

In the **study eye**, ocular AEs up to Month 3 occurred in 27.4% (29/106) of patients in Group I, 13.6% (16/118) of patients in Group II, and 9.4% (5/53) of patients in Group III. The most frequently reported AEs in the study eye in patients in the ranibizumab groups were conjunctival haemorrhage (Group I, 9.4%; Group II, 5.1%; and Group III, 0%), and punctate keratitis (Group I, 5.7%; Group II, 2.5%; and Group III, 3.8%). The number (%) of patients with ocular AEs of the study eye up to Month 3 (at least 2 patients in any group) are presented in Table 9.

Table 9. CRFB002F2301 – Number (%) of patients with ocular AEs of the study eye up to Month 3 (at least 2 patients in any group) by preferred term; safety set.

	Ranibizumab 0.5 mg		vPDT
	Group I by stabilization	Group II by disease activity	Group III
Preferred term	N=106 n (%)	N=118 n (%)	N=53 n (%)
Total	**29 (27.4)**	**16 (13.6)**	**5 (9.4)**
Conjunctival haemorrhage	10 (9.4)	6 (5.1)	0
Punctate keratitis	6 (5.7)	3 (2.5)	2 (3.8)
Dry eye	3 (2.8)	0	0
Eye pain	2 (1.9)	1 (0.8)	0
Intraocular pressure increased	2 (1.9)	2 (1.7)	1 (1.9)

Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg I column.

In the **fellow eye**, the percentage of patients with ocular AEs up to Month 3 were 6.6% (7/106), 6.8% (8/118) and 1.9% (1/9) in Groups I, II, and III, respectively. The only ocular AEs in the fellow eye occurring in 2 or more patients were blepharitis in Group I (1.9%, n=2) compared with no patients in Groups II and III, and dry eye in Group I (1.9%, n=2) compared with 1 (0.8%) patient in Group II and no patients in Group III.

(b) Up to Month 6

In the **study eye**, ocular AEs up to Month 6 were reported in 35.8% (38/106) of patients in Group I and 26.3% (31/118) patients in Group II, while AEs from Month 3 to Month 6 were reported in 29.4% (10/34) patients in Group III with ranibizumab and 21.1% (4/19) in Group III without ranibizumab. The number (%) of patients with ocular AEs of the study eye up to Month 6 (at least 2 patients in any group) are presented in Table 10.

Table 10. CRFB002F2301 – Number (%) of patients with ocular AEs of the study eye up to Month 6 (at least 2 patients in any group) by preferred term; safety set.

	Ranibizumab 0.5 mg		vPDT	
Preferred term	Group I by stabilization N=106 n (%)	Group II by disease activity N=118 n (%)	Group III with 0.5mg Ranibizumab from Month 3 N=34 n (%)	Group III without 0.5mg Ranibizumab from Month 3 N=19 n (%)
Total	**38 (35.8)**	**31 (26.3)**	**10 (29.4)**	**4 (21.1)**
Conjunctival haemorrhage	10 (9.4)	11 (9.3)	0	0
Punctate keratitis	6 (5.7)	3 (2.5)	1 (2.9)	1 (5.3)
Dry eye	4 (3.8)	0	0	0
Eye pain	3 (2.8)	3 (2.5)	0	0
Injection site haemorrhage	3 (2.8)	3 (2.5)	2 (5.9)	0
Vitreous floaters	3 (2.8)	1 (0.8)	0	0
Intraocular pressure increased	2 (1.9)	3 (2.5)	2 (5.9)	0
Retinal tear	2 (1.9)	0	0	0
Conjunctivitis allergic	0	2 (1.7)	0	0
Metamorphopsia	0	2 (1.7)	0	0
Retinal haemorrhage	0	2 (1.7)	0	0

Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg I column.

In the **fellow eye**, the percentage of patients with ocular AEs up to Month 6 in Group I was 14.2% (15/106) and in Group II was 9.3% (11/118). AEs from Month 3 to Month 6 were reported in 11.8% (4/34) of patients in Group III with ranibizumab and 15.8% (3/19) of patients in Group III without ranibizumab. Ocular AEs in the fellow occurring in 2 or more patients in Groups I or II were, respectively: conjunctivitis, n=3 (2.8%) versus 0; dry eyes, n=3 (2.8%); blepharitis, n=2 (1.9%) versus 0; allergic conjunctivitis, 0 versus n=2, 1.7%; and IOP increased 0 versus 2 (1.7%). Ocular AEs in the fellow eye occurring in 2 or more patients in Group III with ranibizumab or Group III without ranibizumab, was, respectively, ocular hypertension 0 versus 2 (10.5%).

(c) Up to Month 12

In the **study eye,** ocular AEs up to Month 12 were reported in 43.4% (46/106) of patients in Group I and 37.3% (44/118) of patients in Group II. Ocular AEs in the study eye from Month 3 to Month 12 were reported in 42.1% (16/38) of patients in Group III with ranibizumab and 26.7% (4/15) of patients in Group III without ranibizumab. The number of patients with ocular AEs in the study eye up to Month 12 are summarised below in Table 11.

Table 11. CRFB002F2301 – Number (%) of patients with ocular AEs of the study eye up to Month 12 (at least 2 patients in any group) by preferred term; safety set.

	Ranibizumab 0.5 mg		vPDT	
	Group I by stabilization	Group II by disease activity	Group III with 0.5mg Ranibizumab from Month 3	Group III without 0.5mg Ranibizumab from Month 3
Preferred term	N=106 n (%)	N=118 n (%)	N=38 n (%)	N=15 n (%)
Total	**46 (43.4)**	**44 (37.3)**	**16 (42.1)**	**4 (26.7)**
Conjunctival haemorrhage	12 (11.3)	12 (10.2)	2 (5.3)	0
Punctate keratitis	8 (7.5)	3 (2.5)	2 (5.3)	0
Vitreous floaters	5 (4.7)	1 (0.8)	0	0
Dry eye	4 (3.8)	2 (1.7)	0	1 (6.7)
Eye pain	4 (3.8)	4 (3.4)	1 (2.6)	1 (6.7)
Injection site haemorrhage	3 (2.8)	3 (2.5)	2 (5.3)	0
Intraocular pressure increased	3 (2.8)	7 (5.9)	4 (10.5)	0
Blepharitis	2 (1.9)	2 (1.7)	0	0
Conjunctivitis	2 (1.9)	1 (0.8)	0	0
Eyelid oedema	2 (1.9)	0	0	0
Retinal tear	2 (1.9)	1 (0.8)	0	0
Cataract	1 (0.9)	2 (1.7)	0	1 (6.7)
Conjunctivitis allergic	1 (0.9)	5 (4.2)	1 (2.6)	0
Ocular hyperaemia	1 (0.9)	2 (1.7)	1 (2.6)	0
Retinal haemorrhage	1 (0.9)	3 (2.5)	0	0
Metamorphopsia	0	3 (2.5)	0	0
Visual impairment	0	0	2 (5.3)	0

- Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg I column.

In the **fellow eye**, ocular AEs occurring up to Month 12 were reported in 22.6% (24/106) of patients in Group I and 18.6% (22/118) of patients in Group II. Ocular AEs in the fellow eye occurring from Month 3 to Month 12 were reported in 23.7% (9/38) of patients in Group III with ranibizumab and 20.0% (3/15) of patients in Group III without ranibizumab. Ocular AEs in the fellow eye reported in 2 or more patients in Group I or II were, respectively: conjunctivitis, n=4 (3.8%) versus 0%; blepharitis, n=3 (2.8%) versus 1 (0.8%); dry eye, n=3 (2.8%) versus n=3 (2.5%); asthenopia, n=2 (1.9%) versus 0; allergic conjunctivitis, n=1 (0.9%) versus n=5 (4.2%); chalazion, 0 versus n=2 (1.7%); ocular hypertension, 0 versus n=2 (1.7%); hordeolum 0 versus n=2 (1.7%); and IOP increased, 0 versus n=2 (1.7%). No ocular AEs in the fellow eye were reported in more than 1 patient in Group III with or without ranibizumab.

8.3.2.1.2. Ocular AEs by maximum severity

In the study eye, ocular AEs occurring up to Month 3 were predominantly mild in severity, with all other events being categorized as moderate. There were no severe AEs reported in any of the three treatment groups. The relevant severity categories (total, mild, moderate, severe; respectively) for each of the three treatment groups were: Group I (n=116) - 29 (27.4%), 27 (25.5%), 2 (1.9%), 0 (0%); Group II (n=106) - 16 (13.6%), 13 (11.0%), 3 (2.5%), 0 (0%); Group III (n=53) – 5 (9.4%), 4 (7.5%), 1 (1.9%), 0 (0%). Similar patterns of ocular AE severity in the study eye were also observed in the treatment groups in the 6 and 12 month data, with most events in each of the groups being categorized as mild.

A total of 18 patients experienced ocular AEs of moderate severity up to Month 12: Group I - punctate keratitis, photopsia, uveitis, visual acuity reduced, vitreous detachment; Group II - vitreous floaters, blepharitis, cataract, retinal haemorrhage, eye haemorrhage, metamorphopsia, ocular hypertension, retinoschisis, IOP increased; Group III with ranibizumab - macular oedema, ocular hypertension; and Group III without ranibizumab - orbital myositis. All except three of the moderate ocular AEs occurred in patients treated with ranibizumab. Up to Month 12, only two events were categorized as severe; dacryocystitis in 1 patient in Group I after Month 6, and conjunctivitis allergic in 1 patient in Group II after Month 3.

8.3.2.1.3. Ocular AEs suspected to be related to study drug and/or injection

(a) Up to Month 3

In the **study eye**, ocular AEs up to Month 3 suspected to be related to study drug and/or ocular injection occurred in 17.9% (19/106) of patients in Group I, 8.5% (10/118) of patients in Group II, and 5.7% (3/53) of patients in Group III. AEs suspected to be related to study drug and/or injection occurring in ≥ 2 patients in any of the three treatment groups were: conjunctival haemorrhage (Group I, 7.5%; Group II, 4.2%; Group III, 0%); punctate keratitis (Group I, 2.8%; Group II, 1.7%; Group III, 3.8%); eye pain (Group I, 1.9%; Group II, 0.8%; Group III, 0%); and IOP increased (Group I, 1.9%; Group II, 0.8%; Group III, 1.9%). The only treatment-related ocular AEs considered to be related to study drug rather than ocular injection were vitreous floaters in 1 (0.8%) patient in Group II. The ocular AEs in the study eye suspected to be related to study drug and/or ocular injection are summarised below in Table 12.

Table 12. CRFB002F2301 – Number (%) of patients with ocular AEs of the study eye up to Month 3, suspected to be related to study drug and/or ocular injection by preferred term; safety set.

	Ranibizumab 0.5 mg		vPDT
	Group I by stabilization N=106	Group II by disease activity N=118	Group III N=53
Preferred term	n (%)	n (%)	n (%)
Total	**19 (17.9)**	**10 (8.5)**	**3 (5.7)**
Conjunctival haemorrhage	8 (7.5)	5 (4.2)	0
Punctate keratitis	3 (2.8)	2 (1.7)	2 (3.8)
Eye pain	2 (1.9)	1 (0.8)	0
Intraocular pressure increased	2 (1.9)	1 (0.8)	1 (1.9)
Conjunctival oedema	1 (0.9)	0	0
Corneal erosion	1 (0.9)	1 (0.8)	0
Injection site haemorrhage	1 (0.9)	1 (0.8)	0
Intracranial pressure increased *	1 (0.9)	0	0
Retinal tear	1 (0.9)	0	0
Uveitis	1 (0.9)	0	0
Vitreous floaters	1 (0.9)	1 (0.8)	0
Vitreous prolapse	1 (0.9)	0	0
Conjunctival hyperaemia	0	0	1 (1.9)

* Intracranial pressure increased" MedDRA code was used for "Intraocular pressure increased".
Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg I column

In the **fellow eye**, no ocular AEs suspected to be related to study drug and/or ocular injection were reported.

(b) Up to Month 6

In the **study eye**, ocular AEs up to Month 6 suspected to be related to study drug and/or ocular injections were reported in 19.8% (21/195) of patients in Group I and 16.1% (19/118) of patients in Group II, while events reported from Month 3 to Month 6 were reported in 11.8% (4/34) of patients in Group III with ranibizumab and 10.5% (2/19) of patients in Group III without ranibizumab.

AEs suspected of being related to study drug and/or ocular injection reported in ≥ 2 patients in the either ranibizumab group (Group I versus Group II) were: conjunctival haemorrhage, 7.5% versus 7.6%; injection site haemorrhage, 2.8% versus 2.5%; punctate keratitis, 2.8% versus 1.7%; eye pain, 1.9% versus 2.5%; and IOP increased, 1.9% versus 0.8%. The only AE suspected of being related to study drug and/or ocular injection in ≥ 2 patients in either Group III with ranibizumab or Group III without ranibizumab was injection site haemorrhage (5.9% versus 0%, respectively). The only treatment-related ocular AEs occurring up to Month 6 suspected to be related to study drug rather than to ocular injection were vitreous floaters in 1 (0.8%) patient in Group II and visual impairment in 1 (2.9%) patient in Group III. The ocular AEs in the

study eye suspected to be related to study drug and/or ocular injection up to Month 6 are summarised below in Table 13.

Table 13. CRFB002F2301 – Number (%) of patients with AEs of the study eye up to Month 6, suspected to be related to study drug and/or ocular injection, by preferred term; safety set.

	Ranibizumab 0.5 mg		vPDT	
	Group I by stabilization	Group II by disease activity	Group III with 0.5mg Ranibizumab from Month 3	Group III without 0.5mg Ranibizumab from Month 3
Preferred term	N=106 n (%)	N=118 n (%)	N=34 n (%)	N=19 n (%)
Total	**21 (19.8)**	**19 (16.1)**	**4 (11.8)**	**2 (10.5)**
Conjunctival haemorrhage	8 (7.5)	9 (7.6)	0	0
Injection site haemorrhage	3 (2.8)	3 (2.5)	2 (5.9)	0
Punctate keratitis	3 (2.8)	2 (1.7)	1 (2.9)	1 (5.3)
Eye pain	2 (1.9)	3 (2.5)	0	0
Intraocular pressure increased	2 (1.9)	1 (0.8)	1 (2.9)	0
Conjunctival oedema	1 (0.9)	0	0	0
Corneal erosion	1 (0.9)	1 (0.8)	0	0
Intracranial pressure increased*	1 (0.9)	0	0	0
Ocular hyperaemia	1 (0.9)	0	0	0
Retinal tear	1 (0.9)	0	0	0
Uveitis	1 (0.9)	1 (0.8)	0	0
Vitreous floaters	1 (0.9)	1 (0.8)	0	0
Vitreous prolapse	1 (0.9)	0	0	0
Conjunctival hyperaemia	0	0	0	1 (5.3)
Iridocyclitis	0	1 (0.8)	0	0
Visual impairment	0	0	1 (2.9)	0

* Intracranial pressure increased" MedDRA code was used for "Intraocular pressure increased".
Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg I column.

In **the fellow eye**, ocular AEs up to Month 6 suspected to be related to study drug and/or ocular injections were reported in 1 (0.8%) patient in Group II (iridocyclitis). The same adverse event (iridocyclitis) was also reported on the same day (Day 113) in the study eye, and was also suspected to be related to the study drug and/or intraocular injection. No other ocular AEs in the fellow suspected to be related to study drug and/or ocular injection were reported up to Month 6.

(c) Up to Month 12

In the **study eye**, ocular AEs suspected to be related to study drug and/or ocular injections were reported up to Month 6 in 24.5% (26/106) of patients in Group I and 20.3% (24/118) of patients in Group II, while events reported from Month 3 to Month 12 were reported in 21.1% (8/38) of patients in Group III with ranibizumab and 13.3% (2/15) of patients in Group III without ranibizumab. Most of the ocular AEs reported up to Month 12 were suspected of being related to ocular injection rather than study drug.

AEs suspected of being related to study drug and/or ocular injection reported in ≥ 2 patients in the either ranibizumab group (Group I versus Group II, respectively) were: conjunctival haemorrhage, 9.4% versus 8.5%; punctate keratitis, 4.7% versus 1.7%; eye pain, 2.8% versus 2.5%; injection site haemorrhage, 2.8% versus 2.5%; and IOP increased, 2.8% versus 4.2%. AEs suspected of being related to study drug and/or ocular injection in ≥ 2 patients in either Group III (with ranibizumab versus without ranibizumab, respectively) were: conjunctival haemorrhage (5.3% versus 0%); punctate keratitis (5.3% versus 0%); injection site haemorrhage (5.3% versus 0%); IOP increased (5.3% versus 0%); and visual impairment (5.3% versus 0%). The ocular AEs in the study eye suspected to be related to study drug and/or ocular injection up to Month 12 are summarised below in Table 14.

Most of the treatment-related ocular AEs occurring up to Month 12 were suspected to be related to ocular injection rather than the study drug. The ocular AEs suspected to be related to study

drug rather than ocular injection were eye pain (1, 0.9%) and IOP increased (1, 0.9%) in Group I, eye irritation (1, 0.8%), metamorphopsia (1, 0.8%), ocular hyperaemia (1, 0.8%), and vitreous floaters (1, 0.8%) in Group II, and visual impairment (2, 5.3%) and ocular hyperaemia (1, 2.6%) in Group III with ranibizumab. In Group III without ranibizumab, all treatment-related ocular AEs were considered to be due to ocular injection rather than study drug.

Table 14. CRFB002F2301 – Number (%) of patients with AEs of the study eye up to Month 12, suspected to be related to study drug and/or ocular injection, by preferred term; safety set.

	Ranibizumab 0.5 mg		vPDT	
	Group I by stabilization	Group II by disease activity	Group III with 0.5mg Ranibizumab from Month 3	Group III without 0.5mg Ranibizumab from Month 3
Preferred term	N=106 n (%)	N=118 n (%)	N=38 n (%)	N=15 n (%)
Total	**26 (24.5)**	**24 (20.3)**	**8 (21.1)**	**2 (13.3)**
Conjunctival haemorrhage	10 (9.4)	10 (8.5)	2 (5.3)	0
Punctate keratitis	5 (4.7)	2 (1.7)	2 (5.3)	0
Eye pain	3 (2.8)	3 (2.5)	1 (2.6)	0
Injection site haemorrhage	3 (2.8)	3 (2.5)	2 (5.3)	0
Intraocular pressure increased	3 (2.8)	5 (4.2)	2 (5.3)	0
Conjunctival oedema	1 (0.9)	0	0	0
Corneal erosion	1 (0.9)	1 (0.8)	0	0
Drug hypersensitivity	1 (0.9)	0	0	0
Injection site pain	1 (0.9)	0	0	0
Intracranial pressure increased*	1 (0.9)	0	0	0
Ocular hyperaemia	1 (0.9)	1 (0.8)	1 (2.6)	0
Retinal tear	1 (0.9)	0	0	0
Uveitis	1 (0.9)	1 (0.8)	0	0
Vitreous floaters	1 (0.9)	1 (0.8)	0	0
Vitreous prolapse	1 (0.9)	0	0	0
Adenoviral conjunctivitis	0	1 (0.8)	0	0
Cataract	0	0	0	1 (6.7)
Conjunctival hyperaemia	0	0	0	1 (6.7)
Eye irritation	0	1 (0.8)	0	0
Iridocyclitis	0	1 (0.8)	0	0
Metamorphopsia	0	1 (0.8)	0	0
Visual impairment	0	0	2 (5.3)	0

* Intracranial pressure increased" MedDRA code was used for "Intraocular pressure increased".
Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg I column.

In **the fellow eye**, there no additional ocular AEs suspected to be related to study drug and/or ocular injection were reported from Month 6 to Month 12. Therefore, reports of ocular AEs suspected to be related for study drug and/or ocular injection at Month 6 and Month 12 were identical for all four treatment groups.

8.3.2.2. Non-ocular adverse events

8.3.2.2.1. Non-ocular adverse events regardless of relationship to treatment

(a) Up to Month 3

Non-ocular AEs regardless of relationship to treatment were reported up to Month 3 in 25.5% of patients in Group I, 25.4% of patients in Group II, and 11.3% of patients in Group III. Non-ocular AEs regardless of relationship to treatment reported in ≥ 2% of patients in either ranibizumab group (Group I versus Group II, respectively) were: nasopharyngitis (4.7% versus 5.1%); headache (3.8% versus 3.4%); back pain (0.9% versus 2.5%); hypertension (0.9% versus 2.5%); and upper respiratory tract infection (0% versus 2.5%). No non-ocular AEs occurred in ≥ 2 patients in Group III. Non-ocular AEs regardless of relationship to treatment reported up to Month 3 (at least 2 patients in any group) are summarised below in Table 15.

Table15. CRFB002F2301 – Number (%) of patients with non-ocular AEs up to Month 3 (at least 2 patients in any group), by preferred term, regardless of relationship to treatment; safety set.

	Ranibizumab 0.5 mg		vPDT
Preferred term	Group I by stabilization N=106 n (%)	Group II by disease activity N=118 n (%)	Group III N=53 n (%)
Total	**27 (25.5)**	**30 (25.4)**	**6 (11.3)**
Nasopharyngitis	5 (4.7)	6 (5.1)	1 (1.9)
Headache	4 (3.8)	4 (3.4)	0
Intervertebral disc protrusion	2 (1.9)	0	0
Pharyngitis	2 (1.9)	0	0
Back pain	1 (0.9)	3 (2.5)	0
Hypertension	1 (0.9)	3 (2.5)	1 (1.9)
Upper respiratory tract infection	1 (0.9)	3 (2.5)	0
Fatigue	0	2 (1.7)	0
Haemorrhoids	0	2 (1.7)	0
Tooth disorder	0	2 (1.7)	0

Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg I column

The majority of non-ocular AEs up to Month 3 in the three treatment groups were rated as mild. The rates for categories of total, mild, moderate, and severe non-ocular AEs, respectively, in patients up to Month 3 in the three treatment groups were: Group 1, 25.5% versus 21.7% versus 3.8% versus 0%; Group II, 25.4% versus 16.9% versus 7.6% versus 0.8%; and Group III, 11.3% versus 11.3% versus 0% versus 0%. Only 1 patient (Group II) was reported to have experienced a severe non-ocular AE (worsening of hypertension on Day 83 in an 83 year female with a history of hypertension, cardiac failure and chronic obstructive pulmonary disease).

(b) Up to Month 6

Non-ocular AEs regardless of relationship to treatment up to Month 6 were reported in 35.8% of patients in Group I and 35.6% of patients in Group II, and from Month 3 to Month 6 in 14.7% of patients in Group III with ranibizumab and 26.3% of patients in Group III without ranibizumab. The general pattern of non-ocular AEs in both Group I and Group II was similar in the Month 3 and Month 6 data. Non-ocular AEs regardless of relationship to treatment occurring up to Month 6 in ≥ 2% of patients in either Group I or Group II, respectively, were: nasopharyngitis (6.6% versus 5.9%); headache (5.7% versus 5.9%); hypertension (1.9% versus 2.5%); back pain (0.9% versus 2.5%); and upper respiratory tract infection (0.9% versus 3.4%). There were no AEs reported in ≥ 2 patients in Group III with or without ranibizumab.

The majority of non-ocular AEs in the 6 Month dataset were rated as mild in each of the four treatment groups. The rates for the categories of total, mild, moderate and severe non-ocular AEs, respectively, in patients up to Month 6 in Group I were 35.7% versus 26.4% versus 8.5% versus 0.9%, and in Group II were 35.6% versus 22.0% versus 11.0% versus 2.5%. The rates for the categories of total, mild, moderate and severe non-ocular AEs, respectively, in patients from Month 3 up to Month 6 in Group III with ranibizumab were 14.7% versus 14.7% versus 0% versus 0%, and in Group III without ranibizumab were 26.3% versus 21.1% versus 5.3% versus 0%.

Up to Month 6, four patients were reported to have experienced severe non-ocular AEs (Group I, 1 patient - gastrointestinal haemorrhage, gastritis erosive, melaena; and Group II, 3 patients – atrial tachycardia, subdural haematoma, hypertension).

(c) Up to Month 12

Non-ocular AEs regardless of relationship to treatment up to Month 12 were reported in 45.3% of patients in Group I and 43.2% of patients in Group II, and from Month 3 to Month 12 in 50.0% of patients in Group III with ranibizumab and 33.3% of patients in Group III without ranibizumab. Non-ocular AEs regardless of relationship to treatment occurring up to Month 6 in

≥ 2% of patients in either Group I or Group II, respectively, were: nasopharyngitis (11.3% versus 10.2%); headache (7.5% versus 9.3%); hypertension (2.8% versus 4.2%); upper respiratory tract infection (2.8% versus 3.4%); urinary tract infection (2.8% versus 2.5%); abdominal pain (2.8% versus 0.8%); back pain (1.9% versus 3.4%); influenza (1.9% versus 3.4%); and bronchitis (0.9% versus 3.4%). Non-ocular AEs regardless of relationship to treatment occurring from Month 3 to Month 6 in ≥ 2 patients in either Group III with ranibizumab or Group III without ranibizumab, respectively, were: nasopharyngitis (1, 2.6% versus 2, 13.3%); hypertension (3, 7.9% versus 0%); and cystitis (2, 5.3% versus 0%).

The majority of non-ocular AEs in the 12 Month dataset were rated as mild in each of the four treatment groups. The rates for the categories of total, mild, moderate and severe non-ocular AEs, respectively, reported in patients up to Month 12 in Group I were 45.3% versus 26.4% versus 16.0% versus 2.8%, and in Group II were 43.2% versus 23.7% versus 14.4% versus 5.1%. The rates for the categories of total, mild, moderate and severe non-ocular AEs, respectively, reported in patients from Month 3 up to Month 12 in Group III with ranibizumab were 50.0% versus 44.7% versus 5.3% versus 0%, and in Group III without ranibizumab were 33.3% versus 26.7% versus 6.7% versus 0%.

Up to Month 12, nine patients were reported to have experienced severe non-ocular AEs (Group I, 3 patients - myocarditis, gastritis erosive, gastrointestinal hemorrhage, melaena, depression; Group II, 6 patients - atrial tachycardia, bronchitis, subdural haematoma muscle spasms, spinal column stenosis, lung adenocarcinoma, hypertension). No Group III patients (with or without ranibizumab) experienced a severe non-ocular AE from Month 3 to Month 12.

8.3.2.2.2. Non-ocular adverse events suspected to be related to study drug and/or ocular injection

(a) Up to Month 3

Non-ocular AEs suspected to be related to study drug and/or ocular injection were reported in 2 patients up to Month 3. Both of these patients were in Group II (n=2, 1.7%) and the events were headache and nausea. No non-ocular AEs suspected to be related to study drug and/or ocular injection were reported in patients in Groups I or III up to Month 3.

(b) Up to Month 6

Non-ocular AEs suspected to be related to study drug and/or ocular injection were reported in 3 patients up to Month 6. The three patients were in Group II (n=3, 2.5%) and the events were headache, hepatic function abnormal and nausea. No non-ocular AEs suspected to be related to study drug and/or ocular injection were reported in patients in Groups I or III up to Month 6.

(c) Up to Month 12

Reports of non-ocular AEs suspected to be related to study drug and/or ocular injection up to Month 12 were identical to those reported up to Month 6.

8.3.3. Deaths and other serious adverse events (SAES)

8.3.3.1. (a) Deaths

No patients died during the 12 month study period.

8.3.3.2. (b) Serious adverse events

Overall, 13 patients experienced at least 1 SAE up to Month 12, 11 of these patients experienced non-ocular SAEs (6 [5.1%] in Group I and 5 [4.2%] in Group II), and 2 of these patients experienced ocular SAEs in the study eye (1 [0.9%] in Group I and 1 [0.8%] in Group II). No patients in Group III experienced SAEs.

Ocular SAEs - Overall, 2 patients were reported to have experienced an ocular SAE in the study eye during the course of this study. One patient in Group I experienced an ocular SAE of mild corneal erosion suspected to be due to ocular injection during the first 3 months of the study

(Day 37). The patient was hospitalized and received concomitant treatment resulting in resolution of the event on Day 43. One patient in Group II experienced an ocular SAE of moderate retinoschisis after Month 6 (Day 309) considered to be unrelated to study drug and/or ocular injection. No action was taken for this SAE. Ocular SAEs in the study eye up to Month 12 are summarised below in Table 16.

Table 16. CEFB002F2301 – Ocular SAEs of the study eye up to Month 12, regardless of relationship to study drug, by preferred term; safety set.

	Ranibizumab 0.5 mg		vPDT	
	Group I by stabilization	Group II by disease activity	Group III with 0.5mg Ranibizumab from Month 3	Group III without 0.5mg Ranibizumab from Month 3
Preferred term	N=106 n (%)	N=118 n (%)	N=38 n (%)	N=15 n (%)
Total	**1 (0.9)**	**1 (0.8)**	**0**	**0**
Corneal erosion	1 (0.9)	0	0	0
Retinoschisis	0	1 (0.8)	0	0

Non-ocular SAEs – Overall, 11 patients were reported to have experienced a non-ocular SAE during the course of the study (see Table 17, below). In the patient in Group I with breast cancer *in situ* the SAE was reported in the first 3 months of treatment. In the patient in Group I with gastritis erosive/gastrointestinal haemorrhage the SAEs occurred between Month 3 and Month 6. In the patients in Group II with atrial tachycardia (1 patient) and subdural haematoma (1 patient) the SAEs occurred between Month 3 and Month 6. All other non-ocular SAEs in both Groups I and II occurred between Month 6 and Month 12. No non-ocular SAEs were reported in Group III.

Table 17. CEFB002F2301 – Non-ocular SAEs of the study eye up to Month 12, regardless of relationship to study drug, by preferred term; safety set.

	Ranibizumab 0.5 mg		vPDT	
	Group I by stabilization	Group II by disease activity	Group III with 0.5mg Ranibizumab from Month 3	Group III without 0.5mg Ranibizumab from Month 3
Preferred term	N=106 n (%)	N=118 n (%)	N=38 n (%)	N=15 n (%)
Total	**6 (5.7)**	**5 (4.2)**	**0**	**0**
Breast cancer in situ	1 (0.9)	0	0	0
Depression	1 (0.9)	0	0	0
Gastritis erosive*	1 (0.9)	0	0	0
Gastrointestinal haemorrhage*	1 (0.9)	0	0	0
Hepatic function abnormal	1 (0.9)	0	0	0
Joint dislocation	1 (0.9)	0	0	0
Myocarditis	1 (0.9)	0	0	0
Atrial tachycardia	0	1 (0.8)	0	0
Lung adenocarcinoma	0	1 (0.8)	0	0
Renal failure chronic	0	1 (0.8)	0	0
Spinal column stenosis	0	1 (0.8)	0	0
Subdural haematoma	0	1 (0.8)	0	0

* Two SAEs were reported for one patient.
Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg I column.

8.4. Treatment discontinuations

No reported AEs resulted in permanent discontinuation of the study drug.

Treatment was interrupted/stopped for reasons other than per-protocol during the course of the study in 7 out of 95 patients (7.4%) in Group I (4 [4.2%] AE or abnormal laboratory test; 2 [2.1%] dosing error; 1 [1.1%] dispensing error), and 11 out of 111 patients (9.9%) in Group II

(2 [1.8%] AE or abnormal laboratory test; 1 [0.9%] lack of efficacy; 5 [4.5%] dosing error; 3 [2.7%] dispensing error).

Treatment was interrupted/stopped for reasons other than per-protocol from Month 3 in 2 out of 15 patients [13.4%] in Group III without ranibizumab (1 [6.7%] dosing error; 1 [6.7%] dispensing error), and no patients (0/32) in Group III with ranibizumab.

8.5. Laboratory tests

8.5.1. Haematology

The study assessed changes in haematology laboratory parameters relating to haemoglobin (Hb), haematocrit (Hct), white cell blood count (WBC), red blood cell count (RBC) and platelet count (that is, absolute change and change from baseline; shift tables; shift tables for critical values). Overall, no clinically relevant changes from baseline over the course of the study were seen in haematology parameters in the treatment groups.

Haematology shift tables for critical values showed that that nearly all patients in the three treatment groups did not experience a shift from normal values at baseline to low or high values in the Month 3, Month 6 or Month 12 datasets. Critical laboratory values were defined for PM patients by Novartis, regardless of whether pre-treatment or post-treatment. Critical haematology values were reported in 6 patients during the course of the study (4 patients in Group 1; 2 patients in Group II), and in these 6 patients a total of 14 haematology values relating to absolute eosinophils, neutrophils, absolute neutrophils, monocytes, and/or platelet counts were listed by the central laboratory as critical laboratory values. However, none of critical values were considered clinically relevant by the investigator or reported as AEs. For 5 of the patients, all values were in the normal range at Visit 9 and/or at the end of study visit. For 1 patient with a low platelet count at Visit 10 (end of study visit for this patient) no follow-up measurement was received.

AEs in the system/organ class (SOC) of 'blood and lymphatic system disorders' occurring from Baseline to Month 12 were reported in 1 (0.9%) patient in Group I (anaemia) and 1 (0.8%) patient in Group II (eosinophilia), and no haematology laboratory AEs were reported in either of the two groups. No 'blood and lymphatic system disorders' AEs or haematology laboratory AEs were reported up to Month 3 in Group III, and from Month 3 to Month 12 in Group III with and without ranibizumab.

8.5.2. Clinical chemistry

The study assessed changes in the standard range of biochemistry laboratory (that is, absolute change and change from baseline; shift tables; shift tables for critical values). Overall, no clinically relevant changes from baseline over the course of the study were seen in biochemistry parameters in the treatment groups.

Critical biochemistry results of increased gamma glutamyltransferase (γ-GT) were reported by the central laboratory for 2 patients in Group II, 1 at Month 3 and 1 at Month 6. The maximum values were 304 U/L at Month 3 for one patient and 347 U/L at Month 6 for one patient. For both patients, laboratory assessments performed at Months 9 and 12 were within the normal range.

During the 12 months of treatment, AEs due to hepatic function abnormal were recorded in 2 patients, 1 in Group I and 1 in Group II. In Group I, 1 patient entered the study with a medical history of 'hepatic function disorder' and liver enzymes increased during the study and were reported as SAEs of hepatic function abnormal. Two (2) patients in Group I and 1 patient in Group II were reported with AEs related to laboratory investigations (increased serum concentrations of AST, ALT, γ-GT, and ALP) in 1 patient, and hepatic enzymes abnormal in 1 patient. One (1) patient was recorded with increased total bilirubin serum concentrations at Months 6 and 9 that decreased by Month 12.

8.5.3. Urinalysis

The study assessed changes in the standard range of urinalysis laboratory parameters (that is, absolute change and change from baseline; shift tables). Overall, no clinically relevant changes from baseline over the course of the study were seen in urinalysis laboratory parameters in the treatment groups.

8.5.4. Electrocardiogram

Electrocardiograms were not reported during this study.

8.5.5. Vital signs

The study assessed changes in systolic/diastolic blood pressure (SPB/DBP) and pulse rate (that is, absolute change and change from baseline; shift tables for abnormal values). Ten (10) patients overall (3, 4, and 3 patients in Groups I, II, and III, respectively) were recorded with an abnormal vital signs value. The reported abnormalities in BP in the 10 patients occurred sporadically, and BP in these patients was within normal limits at nearly all visits. Overall, no clinically significant changes in BP or pulse rate were observed over the course of the study in patients in this study.

8.6. Special safety topics

8.6.1. Intraocular pressure

There was only one patient (Group III without ranibizumab) reported to have experienced an IOP reading of ≥ 30 mmHg in the study eye during the course of the study. The overall range for mean increase from Baseline in IOP post-injection up to Month 12 was 0.2 to 1.8 mmHg in ranibizumab Groups I and II, and 0.7 to 2.2 mmHg in Group III with ranibizumab from Month 3 to Month 12. In Group III, the overall range for mean increase in IOP from Baseline up to Month 3 was 0.7 to 0.9 mmHg with vPDT, and from Month 3 to Month 12 in Group III without ranibizumab the overall range for mean increase in IOP was 0.3 to 2.0 mmHg.

Overall, IOP increase was reported as an AE in 15 patients: 4 patients in Group I, 7 patients in Group II and 4 patients in Group III. In 8 of these 15 patients, 9 AEs of increased IOP suspected to be related to ocular injection were reported (8 mild severity, 1 moderate severity). In 4 patients with 5 treatment-related IOP events, no action was taken and no concomitant medication to reduce the IOP was administered. In the 4 patients with 4 treatment-related IOP events, IOP lowering treatment was administered for one day.

In summary, the reported cases of increased IOP reported post-injection were transient and did not require chronic IOP lowering treatment. Newly diagnosed glaucoma was not reported.

8.6.2. Retinal tear

Patients with PM have a higher risk of retinal tears and retinal detachments, independent of intraocular ocular injections. There were no reported cases of 'retinal detachment'. Three events of mild severity reported by the investigators as 'retinal hole', 'retinal break' and 'retinal tears with operculum' were coded (according to MedDRA) with the preferred term 'retinal tear' and reported for 2 (1.9%) patients in Group I and 1 (0.8%) patient in Group II.

In one patient in Group I, a retinal hole was reported as an AE on Day 21 after the first injection of ranibizumab. This patient had a medical history of glaucoma and pseudophakia (preferred term 'intraocular lens implant'). The retinal hole resolved after 7 days and was assessed as suspected to be related to ocular injection by the reporting investigator. In the other patient in Group 1, a retinal break occurred 49 days after the patient's 4th injection of ranibizumab. The patient was reported with a medical history of keratoconjunctivitis sicca (preferred term 'dry eye'). The retinal break was assessed as not suspected to be related to either ocular injection or study drug. It did not require treatment but was still present at the final ophthalmological examination.

In one patient in Group III, an AE of retinal tear (with operculum) was reported 357 days after the patient's first dose of ranibizumab and 10 months after her last (3rd) dose of ranibizumab. This 41-year-old patient had a history of keratomileusis laser surgery in both eyes nine years ago. The retinal tear was assessed as not suspected to be related to either ocular injection or study drug and resolved within 1 day following laser therapy.

8.6.3. Safety concerns identified in the RMP (Version 11)

8.6.3.1. Ocular safety concerns in the study eye

The study included an assessment of ocular AEs of special concern based on categories of selected preferred term according to the Lucentis RMP (Version 11) at the time of the DBL. Ocular safety concerns were endophthalmitis, intraocular inflammation, cataract, transient IOP increased, deterioration of retinal blood flow, retinal tear, retinal detachment, retinal pigment epithelial tear, vitreous haemorrhage and glaucoma. The ocular safety concern risk categories do not always strictly align with the MedDRA preferred term with the similar or same name. For example, an AE coded to the preferred term 'uveitis' was presented in the RMP risk category of special concern of 'endophthalmitis', although it was not reported as endophthalmitis in the SOC preferred term listings. Similarly, the preferred term 'blepharitis' is included in the risk category of special concern as 'intraocular inflammation', although it would not appear in the AEs listed by SOC in eye disorders but in skin disorders.

Ocular safety concerns in the study eye occurring in patients up to Month 3 were: Group I – endophthalmitis (1, 0.9%), cataract (1, 0.9%), transient IOP increased (2, 1.9%), and retinal tear (1, 0.9%); Group II – transient IOP increased (2, 1.7%%); and Group III – intraocular inflammation (1, 1.9%), and transient IOP increased (1, 1.9%). The ocular safety concerns occurring up to Month 3 reported in no patients in the three treatment groups were deterioration of retinal blood flow, retinal detachment, retinal pigment epithelial tear, vitreous haemorrhage, and glaucoma. Ocular safety concerns occurring in the study eye up to Month 3 are summarised below in Table 18.

Table 18. CRFB002F2301 – Ocular safety concerns in the study eye up to Month 3; safety set.

	Ranibizumab 0.5 mg				Visudyne PDT		
	Group I by stabilization		Group II by disease activity		Group III		Relative Risk
Risk Category	N=106		N=118		N=53		Ranibizumab/vPDT
Preferred term(s)	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	RR (95% CI)
Endophthalmitis							-
Uveitis	1 (0.9)	(0.0,5.1)	0	(0.0,3.1)	0	(0.0,6.7)	
Intraocular inflammation	0	(0.0, 3.4)	0	(0.0, 3.1)	1 (1.9)	(0.0, 10.1)	-
Macular oedema							
Cataract	1 (0.9)	(0.0,5.1)	0	(0.0,3.1)	0	(0.0,6.7)	-
Posterior capsule opacification							
Transient intraocular pressure increased	2 (1.9)	(0.2,6.6)	2 (1.7)	(0.2,6.0)	1 (1.9)	(0.0,10.1)	0.95 (0.11,8.30)
Intraocular pressure increased							
Retinal tear	1 (0.9)	(0.0,5.1)	0	(0.0,3.1)	0	(0.0,6.7)	-
Retinal tear							

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PDT = photodynamic therapy; vPDT = Visudyne (verteporfin) photodynamic therapy.

- Categories are based on sets of preferred terms. The preferred terms shown are those for which events were contained in the Month 6 database.
- MedDRA v14.1 was used for description of safety concerns and for coding of study AEs
- Multiple occurrences of the same event in a patient were counted only once
- 95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation

Ocular safety concerns in the study eye up to Month 6 in patients in Group I were endophthalmitis (1, 0.9%), intraocular inflammation (1, 0.9%), cataract (2, 1.9%), transient IOP increased (2, 1.9%), and retinal tear (2, 1.9%), and in patients in Group II were endophthalmitis (1, 0.8%), intraocular inflammation (1, 0.8%), and transient IOP increased (2, 2.5%). Ocular safety concerns in the study eye from Month 3 up to Month 6 in patients in Group III with ranibizumab were intraocular inflammation (1, 2.9%), cataract (1, 2.9%), and transient IOP increased (2, 5.9%), and in patients in Group III without ranibizumab were glaucoma (1, 5.3%). Ocular safety concerns in the study eye up to Month 3 are summarised below in Table 19.

Table 19. CRFB002F2301 – Ocular safety concerns in the study eye up to Month 6; safety set.

	Ranibizumab 0.5 mg				Visudyne PDT			
	Group I by stabilization		Group II by disease activity		Group III with 0.5mg ranibizumab from Month 3		Group III without 0.5mg ranibizumab from Month 3	
Risk Category	N=106		N=118		N=34		N=19	
Preferred term(s)	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Endophthalmitis Uveitis	1 (0.9)	(0.0,5.1)	1 (0.8)	(0.0,4.6)	0	(0.0,10.3)	0	(0.0,17.6)
Intraocular inflammation Iridocyclitis, macular oedema, ocular hyperemia	1 (0.9)	(0.0,5.1)	1 (0.8)	(0.0,4.6)	1 (2.9)	(0.1,15.3)	0	(0.0,17.6)
Cataract Cataract, posterior capsule opacification	2 (1.9)	(0.2,6.6)	0	(0.0,3.1)	1 (2.9)	(0.1,15.3)	0	(0.0,17.6)
Transient intraocular pressure increased Intraocular pressure increased	2 (1.9)	(0.2,6.6)	3 (2.5)	(0.5,7.3)	2 (5.9)	(0.7,19.7)	0	(0.0,17.6)
Retinal tear Retinal tear	2 (1.9)	(0.2,6.6)	0	(0.0,3.1)	0	(0.0,10.3)	0	(0.0,17.6)
Glaucoma Ocular hypertension	0	(0.0, 3.4)	0	(0.0, 3.1)	0	0.0 (10.3)	1 (5.3)	(0.1, 26.0)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PDT = photodynamic therapy.

- Categories are based on sets of preferred terms. The preferred terms shown are those for which events were contained in the Month 6 database.
- MedDRA v14.1 was used for description of safety concerns and for coding of study AEs
- Multiple occurrences of the same event in a patient were counted only once
- 95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation

Ocular safety concerns in the study eye up to Month 12 in patients in Group I were endophthalmitis (1, 0.9%), intraocular inflammation (1, 0.9%), cataract (3, 2.8%), transient IOP increased (3, 2.8%), and retinal tear (2, 1.9%), and in patients in Group II were endophthalmitis (1, 0.8%), intraocular inflammation (4, 3.4%), cataract (2, 1.7%), transient IOP increased (7, 5.9%), retinal tear (1, 0.8%), and glaucoma (1, 0.8%). Ocular safety concerns in the study eye from Month 3 up to Month 12 in patients in Group III with ranibizumab were intraocular inflammation (2, 5.3%) cataract (1, 2.6%), and transient IOP increased (4, 10.5%), and glaucoma (1, 2.6%), and in patients Group III without ranibizumab were cataract (1, 6.7%). Up to Month 12, there had been no reports of ocular safety concerns in the study of eye of deterioration of retinal blood flow, retinal detachment, retinal pigment epithelial tear, or vitreous haemorrhage in patients in either ranibizumab group (that is, Group I or Group II). Ocular safety concerns in the study eye up to Month 3 are summarised below in Table 20.

Table 20. CRFB002F2301 – Ocular safety concerns in the study eye up to Month 6; safety set.

	Ranibizumab 0.5 mg				Visudyne PDT			
	Group I by stabilization		Group II by disease activity		Group III with 0.5mg ranibizumab from Month 3		Group III without 0.5mg ranibizumab from Month 3	
Risk Category	N=106		N=118		N=38		N=15	
Preferred term(s)	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Endophthalmitis Uveitis	1 (0.9)	(0.0,5.1)	1 (0.8)	(0.0,4.6)	0	(0.0,9.3)	0	(0.0,21.8)
Intraocular inflammation Iridocyclitis, macular oedema, ocular hyperemia	1 (0.9)	(0.0,5.1)	4 (3.4)	(0.9, 8.5)	2 (5.3)	(0.6,17.7)	0	(0.0,21.8)
Cataract Cataract, cataract subcapsular,posterior capsule opacification	3 (2.8)	(0.6,8.0)	2 (1.7)	(0.2,6.0)	1 (2.6)	(0.1,13.8)	1 (6.7)	(0.2,31.9)
Transient intraocular pressure increased Intraocular pressure increased[a]	3 (2.8)	(0.6,8.0)	7 (5.9)	(2.4,11.8)	4 (10.5)	(2.9,24.8)	0	(0.0,21.8)
Retinal tear Retinal tear	2 (1.9)	(0.2,6.6)	1 (0.8)	(0.0,4.6)	0	(0.0,9.3)	0	(0.0,21.8)
Glaucoma Ocular hypertension	0	(0.0, 3.4)	1 (0.8)	(0.0,4.6)	1 (2.6)	(0.1,13.8)	0	(0.0,21.8)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PDT = photodynamic therapy.

- Categories are based on sets of preferred terms. The preferred terms shown are those for which events were contained in the Month 6 database.
- MedDRA v14.1 was used for description of safety concerns and for coding of study AEs
- Multiple occurrences of the same event in a patient were counted only once
- 95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation

a One event of transient intraocular pressure increased is not included in this table as it was coded as intracranial pressure increased.

8.6.3.2. Ocular safety concerns in the fellow eye

Ocular safety concerns in the fellow eye in patients up to Month 3 were: Group I - cataract (1, 0.9%); Group II – transient IOP increased (1, 0.8%) and deterioration of retinal blood flow (1, 0.8%); and Group III – no events.

Ocular safety concerns up to Month 6 in patients in Group I were cataract (1, 0.9%), and in patients in Group II were intraocular inflammation (1, 0.8%), transient IOP increased (2, 1.7%), deterioration of retinal blood flow (1, 0.8%), and glaucoma (1, 0.8%). Ocular safety concerns in the fellow eye from Month 3 up to Month 6 in patients in Group III with ranibizumab were transient IOP increased (1, 2.9%), and in patients in Group III without ranibizumab were glaucoma (2, 10.5%).

Ocular safety concerns in the fellow eye up to Month 12 in patients in Group I were intraocular inflammation (1, 0.9%), cataract (2, 1.9%), and in patients in Group II were intraocular inflammation (1, 0.8%), cataract (1, 0.8%), transient IOP increased (2, 1.7%), deterioration of retinal blood flow (1, 0.8%), and glaucoma (2, 1.7%). Ocular safety concerns in the fellow eye from Month 6 up to Month 12 in patients in Group III with ranibizumab were intraocular inflammation (2, 5.3%), cataract (1, 2.6%), transient IOP increased (4, 10.5%), and glaucoma (1, 2.6%), and in patients in Group III without ranibizumab were cataract (1, 6.7%).

8.6.3.3. Systemic safety concerns (identified in RMP)

The study included an assessment of systemic AEs of special concern based on categories of selected preferred term according to the Lucentis RMP (version 11) at the time of the DBL. The systemic safety concerns were hypersensitivity, hypertension, non-ocular haemorrhage, proteinuria, myocardial infarction, other arterial thromboembolic events, and venous thromboembolic events.

Systemic safety concerns up to Month 3 in patients in the three treatment groups were: Group 1 – hypersensitivity (3, 2.8%) and hypertension (1, 0.9%); Group II – hypersensitivity (2, 1.7%), hypertension (3, 2.5%), and non-ocular haemorrhage (1, 1.7%); and Group III – hypertension (1, 1.9%). There had been no reports in the three treatment groups up to Month 3 of systemic safety concerns of proteinuria, myocardial infarction, other arterial thromboembolic events, and venous thromboembolic events. Systemic AEs of special interest up to Month 3 are summarised below in Table 21.

Table 21. CRFB002F2301 - Systemic safety concerns up to Month 3; safety set.

	Ranibizumab 0.5 mg				Visudyne PDT		
	Group I by stabilization N=106		Group II by disease activity N=118		Group III N=53		Relative Risk
Risk Category Preferred term(s)	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	Ranibizumab/vPDT RR (95% CI)
Hypersensitivity Corneal oedema, conjunctivitis allergic, eye pruritus, conjunctival oedema, rash, dermatitis allergic	3 (2.8)	(0.6,8.0)	2 (1.7)	(0.2,6.0)	0	(0.0,6.7)	-
Hypertension Hypertension	1 (0.9)	(0.0,5.1)	3 (2.5)	(0.5,7.3)	1 (1.9)	(0.0,10.1)	0.95 (0.11, 8.30)
Non-ocular haemorrhage Rectal haemorrhage, gastrointestinal haemorrhage	0	(0.0, 3.4)	2 (1.7)	(0.2, 6.0)	0	(0.0, 6.7)	-

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PDT = photodynamic therapy; vPDT = Visudyne (verteporfin) photodynamic therapy.

- Includes ocular and non-ocular AEs
- Categories are based on sets of preferred terms. The preferred terms shown are those for which events were contained in the Month 6 database.
- MedDRA v14.1 was used for description of safety concerns and for coding of study AEs
- Multiple occurrences of the same event in a patient were counted only once
- 95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation

Systemic safety concerns up to Month 6 in patients in Group I were hypersensitivity (3, 2.8%), hypertension (2, 1.9%), and non-ocular haemorrhage (1, 0.9%), and in patients in Group II were hypersensitivity (4, 3.4%), hypertension (3, 2.5%), and non-ocular haemorrhage (4, 3.4%). Systemic safety concerns from Month 3 up to Month 6 in patients in Group III with ranibizumab were hypersensitivity (1, 2.9%) and hypertension (1, 2.9%), while no events were reported in Group III without ranibizumab.

Systemic safety concerns up to Month 12 in patients in Group I were hypersensitivity (8, 7.5%), hypertension (4, 3.8%), non-ocular haemorrhage (2, 1.9%) and other arterial thromboembolic events (1, 0.9%), and in Group II were hypersensitivity (9, 7.6%), hypertension (5, 4.2%) and non-ocular haemorrhage (5, 4.2%). Systemic safety concerns from Month 3 up to Month 12 in patients in Group III with ranibizumab were hypersensitivity (2, 5.3%) and hypertension (3, 7.9%), while no events were reported in Group III without ranibizumab. In the two ranibizumab groups (Group I and Group II), there had been no reports of systemic AEs of special interest up to Month 12 of proteinuria, myocardial infarction, or venous thromboembolic events.

8.6.4. Safety in special groups

8.6.4.1. Age

Ocular safety concerns in the study eye and systemic safety concerns were compared in patients aged < 50 years (84/277, 30%) and ≥ 50 years (193/277, 70%), and in patients < 65 years (199/277, 72%) and ≥ 65 years (78/277, 28%). There were no marked differences in ocular safety concerns in the study eye and systemic safety concerns between patients aged < 50 and ≥ 50 years, or between patients aged < 65 and ≥ 65 years.

8.6.4.2. Sex

Ocular safety concerns in the study eye and systemic safety concerns were compared in male and female patients. There were notably more females in the study compared with males (75.5%, 209/277 and 24.5%, 68/277, respectively). The safety differences of note between the two sexes were:

- Ocular safety concerns in the study eye up to Month 3 occurred more frequently in females compared with males. In males, no ocular safety concerns up to Month 3 were reported in Groups I and II, and ocular safety concerns were reported in 2 patients in Group III (1, 6.7%, intraocular inflammation; 1, 6.7%, transient IOP increased). In females, ocular safety concerns were reported in 5 patients in Group I (2, 2.4%, transient IOP increased; 1, 1.2%, endophthalmitis; 1, 1.2%, cataract; 1, 1.2%, retinal tear), 2 patients in Group II (2, 2.2%, transient IOP increased), and no patients in Group III.
- All systemic safety concerns up to Month 3 in Groups I, II, and III were reported in females and none were reported in males. The systemic safety concerns up to Month 3 in female patients were: Group I – hypersensitivity (3, 3.7%) and hypertension (1, 1.7%); Group II – hypersensitivity (2, 2.2%), hypertension (3, 3.4%), and non-ocular haemorrhage (2, 2.2%); and in Group III – hypertension (1, 2,6%).

The observed differences between males and females should be interpreted cautiously due to the small number of total events reported and the imbalance in patient numbers between the two subgroups.

8.7. Supportive Phase II study CRFB002AGB10

The single country (UK), multicentre (12 centres), open-label, single-arm, supportive Phase II study of 12 months duration included safety data from 65 patients with visual impairment due to CNV secondary to PM. All 65 patients received ranibizumab 0.5 mg IVT injection at baseline. AEs in the study were categorized as ocular (presumably in the study eye) and non-ocular. All safety data in this study should be interpreted cautiously due to the absence of a control group.

By the Month 12 visit, the cumulative number of treatments was one (21.5%), two (18.5%) or three (16.9%), with 28 patients (43.1%) receiving four or more treatments in total. Two patients received an injection at each of the 11 successive post-baseline monthly study visits (that is, 12 injections in total).

The overall incidence of AEs in the 65 patients was 70.8% (n=46). AEs (preferred term) reported in ≥ 5% of patients were eye pain (10.8%, n=7), nasopharyngitis (9.3%, n=6); lower respiratory tract infection (7.7%, n=5), back pain (6.2%, n=4), conjunctival haemorrhage (6.2%, n=4), cough (6.2%m n=4), fall (6.2%, n=4), headache (6.2%, n=4), vitreous floaters (6.2%, n=4), foreign body sensation in eyes (4.6%, n=3), hypertension (4.6%, n=3), arthralgia (3.1%, n=2), dizziness (3.1%, n=3), gout (3.1%, n=3), influenza (3.1%, n=3), intraocular pressure increased (3.1%, n=3), metamorphopsia (3.1%, n=3), migraine (3.1%, n=3) musculoskeletal pain (3.1%, n=3), procedural nausea (3.1%, n=3), sinusitis (3.1%, n=3), tooth extraction (3.1%, n=3), upper respiratory infection (3.1%, n=3), vision blurred (3.1%, n=3), and visual acuity reduced (3.1%, n=3). A patient with multiple occurrences of an AE was counted only once in the AE category.

In the 29 patients with one or more ocular AEs, the severity of AEs was mild in 22 (33.8%) patients, moderate in 5 (7.7%), and severe in 2 (3.1%). The AEs graded moderate were normal tension glaucoma, reduced VA, corneal abrasion, increased IOP and trabeculectomy. AEs graded severe were CNV and endophthalmitis. For non-ocular AEs, AEs were graded mild, moderate and severe in 25 (38.5%) patients, 12 (18.5%) patients and 2 (3.1%) patients.

Ocular AEs with a suspected relation to study drug were reported in 4 (6.2%) patients: conjunctival haemorrhage (1.5%, n=1), vitreous floaters (3.1%, n=2) and endophthalmitis (1.5%, n=1). There were no non-ocular AEs suspected to be related to the study drug.

There were no deaths during the course of the study. Serious adverse events (SAEs) reported during the study or within the 30-day follow-up period occurred in 3 (4.6%) patients: endophthalmitis (1.5%, n=1), joint dislocation (1.5%, n=1), and depression (1.5%, n=1). The one case of endophthalmitis in a 73 year old female patient required hospital treatment and was considered to be treatment-related, the two other cases (joint dislocation and depression) were considered unrelated to treatment. No patient required discontinuation, dose adjustment or interruption of study drug due to AEs suspected to be related to study drug.

No patients permanently discontinued treatment due to AEs. One (1.5%) patient experienced an AE (reduced VA) that resulted in study drug dose adjustment or interruption. In this patient, a sudden drop in vision was reported, which was of mild severity and was not suspected to be related to study drug. In total, 29 patients required significant additional therapy for AEs, regardless of study drug relationship. These included treatment for 8 ocular AEs (one case each of conjunctivitis, eye inflammation, eye lid pain, foreign body sensation in eyes, hyphaema, normal tension glaucoma, ocular discomfort, punctate keratitis and ulcerative keratitis).

There were no clinically relevant changes in sitting pulse, sitting systolic blood pressure or sitting diastolic blood pressure from baseline through Month 12, including assessments based on post-injection measurements of vital signs. There were 9 patients with abnormalities in vital signs reported at one or more visits. In none of these patients were the vital sign abnormalities persistent, and the reported abnormalities are considered to be clinically insignificant.

An assessment of baseline versus worst post-baseline inflammation grade for the study eye indicated no concerns for any of the five parameters evaluated (anterior chamber flare, anterior chamber cells, conjunctiva, vitreous cells and vitreal haemorrhage density), with only rare cases of increased severity of inflammation. Fluorescein angiography and fundus photography of the study eye showed that subretinal or intraretinal haemorrhage was present in 41 patients at baseline but was observed in only 13 patients during the study; one de novo case was observed. Slit lamp examination showed no increase in the number of patients with clinically significant abnormalities during the study for any parameter (lids, cornea, conjunctiva, iris, lens, anterior chamber or other). Ophthalmic examination showed the number of patients with clinically significant abnormalities of the vitreous, retina, macula, choroids or optic nerve, or optic nerve

pallor, to be 0, 6, 61, 5, 0 and 0, respectively, at baseline, compared with 2, 4, 41, 9, 2 and 1, respectively, at Month 12.

Mean IOP in the study eye remained stable throughout the study, with no consistent change from baseline at successive study visits when measured either pre-injection or post-injection.

No clinical laboratory assessments were undertaken in the study. No assessment of RMP ocular or systemic safety concerns were undertaken in this study.

8.8. Post-marketing experience

Lucentis had not been marketed in any country for the treatment of visual impairment due to CNV secondary to PM at the time of the submission. Lucentis was first registered in the US on 30 June 2006 for wet AMD by Genentech. Novartis is currently the Marketing Authorization Holder for wet AMD in more than 100 countries and for DME and RVO in more than 80 countries. Cumulatively, up to 30 June 2012, the safety database of spontaneous reports, including reports from health care professionals, has been provided in Periodic Safety Update Report 9 (PSUR 9). It is assumed that this PSUR has been previously evaluated by the TGA, as it was not included in the submitted data package for the extension of indication. The RMP provided with the submission indicates that the estimated post-marketing exposure to Lucentis in patient treatment years (up to and including PSUR 9) was 1,648,200 (calculated by assuming 6 vials per patient per year).

8.9. Overall conclusions on safety

The safety of ranibizumab for the treatment of visual impairment due to CNV secondary to PM is based primarily on the data from the randomised, active-controlled, double-masked, pivotal Phase III study (CRFB002F2301), supported by the data from single-arm Phase II study. Overall, it is considered that the safety of ranibizumab for the proposed indication is satisfactory and is consistent with the known safety profile for ranibizumab for the approved indications (that is, wet AMD, VA due to DME, and VA due to macular oedema secondary to RVO). The safety data for the proposed indication do not give rise to new safety concerns or safety signals for treatment with ranibizumab administered by IVT injection. The safety data from the pivotal Phase III study are reviewed below. No unexpected new safety data emerged in the supportive Phase II study, and the results of this study have not been reviewed below but have been presented above.

8.9.1. Pivotal Phase III study (CRFB002F2301)

The safety set in the pivotal study included all 277 randomised patients (n=106, Group I, ranibizumab/stabilization; n=118, Group II, ranibizumab/disease activity; n=53, Group III, vPDT). From Month 3 through to Month 12, patients in Group III received treatment with ranibizumab or without ranibizumab (n= 38 and n=15, respectively).

The mean number of ranibizumab injections up to Month 3 was higher in patients in Group I (2.5 injections) than in Group II (1.8 injections). On average, patients in ranibizumab Groups I and II had received 3.5 and 2.5 injections, respectively, from Baseline up to Month 6, and 4.6 and 3.5 injections, respectively, from Baseline up to Month 12.

In the patients randomised to Group III (vPDT), 64.1% (34/53) were treated with ranibizumab from Month 3 to Month 6 and 71.7% (38/53) from Month 3 up to Month 12. The mean number of ranibizumab injections in Group III from Month 3 up to Month 6 was 1.9 injections and 3.2 injections from Month 3 up to Month 12.

8.9.1.1. Ocular AEs in the study eye regardless of relationship to study drug

In the study eye, ocular AEs from Baseline up to Month 3, regardless of the relationship to the study drug were, were reported in 27.4% (29/106) of patients in Group I, 13.6% (16/118) of

patients in Group II, and 9.4% (5/53) of patients in Group III. The ocular AEs in the study eye occurring in ≥ 2% of patients in at least one of the three treatment groups (Group I versus Group II versus Group III), respectively, were conjunctival haemorrhage (9.4% versus 5.1% versus 0%), punctate keratitis (5.7% versus 2.5% versus 3.8%), and dry eye (2.8% versus 0% versus 0%). From Baseline up to Month 3, ocular AEs in the study eye occurred more frequently in the two ranibizumab groups (Group I and II) than in the vPDT group (Group III). In addition, AEs were reported more frequently in Group I compared with Group II (2.5 versus 1.8 injections, respectively), suggesting that increased number of injections and/or dose of ranibizumab are associated with more frequent AEs.

From Baseline up to 6 Month and from Baseline up to 12 Month datasets, ocular AEs in the study eye, irrespective of the relationship to the study drug, occurred more frequently in patients in Group I than in Group II. From Baseline up to Month 12, ocular AEs in the study eye were reported in 43.4% of patients in Group I and 37.3% of patients in Group II. Ocular AEs in the study eye reported in ≥ 2% of patients in either Group I or Group II, respectively, were conjunctival haemorrhage (11.3% versus 10.2%), punctate keratitis (7.5% versus 2.5%), vitreous floaters (4.7% versus 0.8%), dry eye (3.8% versus 1.7%), eye pain (3.8% versus 3.4%), injection site haemorrhage (2.8% versus 2.5%), IOP increased (2.8% versus 5.9%), conjunctivitis allergic (0.9% versus 4.2%), retinal haemorrhage (0.9% versus 2.5%), and metamorphopsia (0% versus 2.5%).

In the Month 3 to Month 6 and the Month 3 to Month 12 datasets, ocular AEs in the study eye, irrespective of the relationship to the study drug, occurred more frequently in patients in Group III with ranibizumab compared with patients in Group III without ranibizumab. These results suggest that ranibizumab is associated with ocular AEs in the treated eye. From Month 3 up to Month 12, ocular AEs in the study eye were reported in 42.1% of patients in Group III with ranibizumab and 26.7% of patients in Group III without ranibizumab. Ocular AEs in the study eye reported in ≥ 2% of patients in Group III with ranibizumab or without ranibizumab, respectively, were IOP increased (10.5% versus 0%), conjunctival haemorrhage (5.3% versus 0%), punctate keratitis (5.3% versus 0%), injection site haemorrhage (5.3% versus 0%), visual impairment (5.3% versus 0%), eye pain (2.6% versus 6.7%), conjunctivitis allergic (2.6% versus 0%), ocular hyperaemia (2.6% versus 0%), dry eye (0% versus 6.7%), and cataract 0% versus 6.7%).

Most of the ocular AEs in the study eye recorded throughout the study were rated as mild or moderate in severity except for two patients who reported severe AEs (Group I – one patient, dacryocystitis after Month 6; Group II – one patient, conjunctivitis allergic after Month 3).

8.9.1.2. Ocular AEs in the study eye suspected to be related to study drug and/or ocular injection

Overall, the majority of treatment-related ocular AEs in the study eye were suspected to be related to ocular injection rather than study drug. From Baseline up to Month 3, ocular AEs in the study eye suspected to be related to study drug and/or ocular injection occurred more frequently in patients in both ranibizumab treatment groups (Group I and II) than in patients in the vPDT treatment group (Group III). During the 12 Month treatment period ocular AEs in the study eye suspected to be related to the study drug and/or ocular injection occurred more frequently in Group I than in Group II, and most likely reflects the increased mean number of ranibizumab injections administered to patients in Group I compared with patients in Group II (mean of 4.6 versus 3.5, respectively). Similarly, from Month 3 to Month 12 ocular AEs in the study eye suspected to be related to the study drug/and or ocular injection were reported more frequently in patients in Group III with ranibizumab (mean of 3.2 injections) than in patients in Group III without ranibizumab.

From Baseline up to Month 3, ocular AEs in the study eye suspected to be related to study drug and/or ocular injection were reported in 17.9% of patients in Group I, 8.5% of patients in Group II, and 5.7% of patients in Group III. The ocular AEs in the study eye suspected to be related to

study drug and/or ocular injection occurring in ≥ 2% of patients in at least one of the three treatment groups (Group I versus Group II versus Group III), respectively, were conjunctival haemorrhage (7.5% versus 4.2% versus 0%) and punctate keratitis (2.8% versus 1.7% versus 3.8%).

In the from Baseline up to 6 Month and from Baseline up to 12 Month datasets, ocular AEs in the study eye suspected to be related to study drug and/or ocular injection occurred more frequently in patients in Group I than in Group II. From Baseline up to Month 12, ocular AEs in the study eye suspected to be related to study drug and/or ocular injection were reported in 24.5% of patients in Group I and 20.3% of patients in Group II. Ocular AEs in the study eye suspected to be related to study drug and/or intraocular injection reported in ≥ 2% of patients in either Group I or Group II, respectively, from Baseline up to Month 12 were conjunctival haemorrhage (9.4% versus 8.5%), punctate keratitis (4.7% versus 1.7%), eye pain (2.8% versus 2.5%), injection site haemorrhage (2.8% versus 2.5%), and IOP increased (2.8% versus 4.2%).

In the Month 3 to Month 6 and the Month 3 to Month 12 datasets, ocular AEs in the study eye suspected to be related to study drug and/or ocular injection occurred more frequently in patients in Group III with ranibizumab compared with patients in Group III without ranibizumab. From Month 3 up to Month 12, ocular AEs in the study eye were reported in 21.1% of patients in Group III with ranibizumab and 13.3% of patients in Group III without ranibizumab. Ocular AEs in the study eye reported in ≥ 2% of patients in either Group III with ranibizumab or Group III without ranibizumab, respectively, from Month 3 to Month 12 were conjunctival haemorrhage (5.3% versus 0%), punctate keratitis (5.3% versus 0%), injection site haemorrhage (5.3% versus 0%), IOP increased (5.3% versus 0%), eye pain (2.6% versus 0%), cataract (0% versus 6.7%), and conjunctival hyperaemia (0% v 6.7%).

8.9.1.3. Ocular safety concerns in the study eye (identified in the RMP)

From Baseline up to Month 3, ocular safety concerns in the study eye in patients in the three treatment groups were: Group I – endophthalmitis (1, 0.9%)[3], cataract (1, 0.9%), transient IOP increased (2, 1.9%), and retinal tear (1, 0.9%); Group II – transient IOP increased (2, 1.7%); and Group III – intraocular inflammation (1, 1.9%) and transient IOP increased (1, 1.9%). No patients in the three treatment groups were reported to have experienced ocular safety concerns in the study eye from Baseline up to Month 3 of deterioration of retinal blood flow, retinal detachment, retinal pigment epithelial tear, vitreous haemorrhage, or glaucoma.

Ocular safety concerns in the study eye from Baseline up to Month 6 in patients in Group I were endophthalmitis (1, 0.9%)[4], intraocular inflammation (1, 0.9%), cataract (2, 1.9%), transient IOP increased (2, 1.9%), and retinal tear (2, 1.9%), and in patients in Group II were endophthalmitis (1, 0.8%), intraocular inflammation (1, 0.8%), and transient IOP increased (2, 2.5%). Ocular safety concerns in the study eye from Month 3 up to Month 6 in patients in Group III with ranibizumab were intraocular inflammation (1, 2.9%), cataract (1, 2.9%), and transient IOP increased (2, 5.9%), and in patients in Group III without ranibizumab were glaucoma (1, 5.3%)[5].

Ocular safety concerns in the study eye from Baseline up to Month 12 in patients in Group I were endophthalmitis (1, 0.9%)[6], intraocular inflammation (1, 0.9%), cataract (3, 2.8%), transient IOP increased (3, 2.8%), and retinal tear (2, 1.9%), and in patients in Group II were endophthalmitis (1, 0.8%), intraocular inflammation (4, 3.4%), cataract (2, 1.7%), transient IOP increased (7, 5.9%), retinal tear (1, 0.8%), and glaucoma (1, 0.8%)[7]. Ocular safety concerns in the study eye from Month 3 up to Month 12 in patients in Group III with ranibizumab were

[3] Erratum: : endophthalmitis category (PT uveitis: 1, 0.9%)
[4] Erratum: : endophthalmitis category (PT uveitis: 1, 0.9%)
[5] Erratum: glaucoma category (PT ocular hypertension: 1, 5.3%)
[6] Erratum: endophthalmitis category (PT uveitis: 1, 0.9%)
[7] Erratum: glaucoma category (PT ocular hypertension: 1, 0.8%)

intraocular inflammation (2, 5.3%) cataract (1, 2.6%), transient IOP increased (4, 10.5%), and glaucoma (1, 2.6%)[8], and in patients in Group III without ranibizumab were cataract (1, 6.7%).

From Baseline up to Month 12, there had been no reports in Group I or II of ocular safety concerns in the study of eye of deterioration of retinal blood flow, retinal detachment, retinal pigment epithelial tear, or vitreous haemorrhage.

8.9.1.4. Non-ocular adverse events

From Baseline up to Month 3, non-ocular AEs, regardless of relationship to treatment, were reported in a similar percentage of patients in the two ranibizumab groups (Group I, 25.5%; Group II, 25.4%), and more frequently than in the vPDT group (Group III, 11.3%). Non-ocular AEs, regardless of relationship to treatment, occurring in ≥ 2% of patients in at least one of the three treatment groups (Group I versus Group II versus Group III), respectively, were nasopharyngitis (4.7% versus 5.1% versus 1.9%), headache (3.8% versus 3.4% versus 0%), back pain (0.9% versus 2.5% versus 0%), hypertension (0.9% versus 2.5% versus 1.9%), and upper respiratory tract infection (0.9% versus 2.5% versus 0%).

In the from Baseline up to 6 Month and the from Baseline up to 12 Month datasets, non-ocular AEs, irrespective of relationship to study drug, occurred in a similar proportion of patients in Groups I and II. From Baseline up to Month 12, non-ocular AEs were reported in 35.8% of patients in Group I and 35.6% of patients in Group II. Non-ocular AEs reported in ≥ 2% of patients in either Group I or Group II, respectively, from Baseline to Month 12 were nasopharyngitis (6.6% versus 5.9%), headache (5.7% versus 5.9%), hypertension (1.9% versus 2.5%), back pain (0.9% versus 2.5%), and upper respiratory tract infection (0.9% versus 3.4%)[9].

From Month 3 to Month 6, non-ocular AEs, irrespective of relationship to drug, occurred more frequently in Group III without ranibizumab compared with ranibizumab (that is, 26.3% versus 14.7%, respectively), while from Month 3 to Month 12 the reverse relationship was seen for Group III (that is, 50.0% with ranibizumab versus 33.3% without ranibizumab).

In all treatment groups in all datasets, non-ocular AEs suspected to be related to study drug and/or ocular injections were reported infrequently.

8.9.1.5. Systemic safety concerns (identified in the RMP)

Systemic safety concerns from Baseline up to Month 3 in patients in the three treatment groups were: Group 1 – hypersensitivity (3, 2.8%) and hypertension (1, 0.9%); Group II – hypersensitivity (2, 1.7%), hypertension (3, 2.5%), and non-ocular haemorrhage (1, 1.7%); and Group III – hypertension (1, 1.9%). There were no reports in the three treatment groups from Baseline up to Month 3 of systemic safety concerns of proteinuria, myocardial infarction, other arterial thromboembolic events, and venous thromboembolic events.

Systemic safety concerns from Baseline up to Month 12 in patients in Group I were hypersensitivity (8, 7.5%), hypertension (4, 3.8%), non-ocular haemorrhage (2, 1.9%) and other arterial thromboembolic events (1, 0.9%), and in Group II were hypersensitivity (9. 7.6%), hypertension (5, 4.2%) and non-ocular haemorrhage (5, 4.2%). Systemic safety concerns from Month 3 up to Month 12 in patients in Group III with ranibizumab were hypersensitivity (2, 5.3%) and hypertension (3, 7.9%), while in Group III without ranibizumab no events were reported. In the two ranibizumab groups (Group I and Group II), there had been no reports of

[8] Erratum: glaucoma category (PT ocular hypertension: 1, 2.6%).

[9] Erratum: From Baseline up to Month 12, non-ocular AEs were reported in 45.3% of patients in Group I and 43.2% of patients in Group II. Non-ocular AEs reported in ≥ 2% of patients in either Group I or Group II, respectively, from Baseline to Month 12 were nasopharyngitis (11.3% versus 10.2%), headache (7.5% versus 9.3%), hypertension (2.8% versus 4.2%), back pain (1.9% versus 3.4%), upper respiratory tract infection (2.8% versus 3.4%), urinary tract infection (2.8% versus 2.5%) and abdominal pain (2.8% versus 0.8%).

systemic safety concerns from Baseline up to Month 12 of proteinuria, myocardial infarction, or venous thromboembolic events.

8.9.1.6. Death, serious adverse events, and discontinuations due to adverse events

No patients died during the 12 month study period. Overall, 13 patients experienced at least 1 SAE during the course of the study, 11 of these patients experienced non-ocular SAEs (6 [5.1%] patients in Group I and 5 [4.2%] patients in Group II) and 2 of these patients experienced ocular SAEs in the study eye (1 [0.9%] in Group I and 1 [0.8%] in Group II). No patients in Group III experienced SAEs.

Two (2) patients were reported to have experienced an ocular SAE in the study eye during the course of the study. One patient in Group I experienced an ocular SAE of mild corneal erosion suspected to be due to ocular injection during the first 3 months of the study (Day 37). The patient was hospitalized and received concomitant treatment resulting in the resolution of the event on Day 43. One patient in Group II experienced and ocular SAE of moderate retinoschisis after Month 6 (Day 309) considered to be unrelated to the study drug and/or the ocular injection. No action was taken for this SAE.

No SAEs of endophthalmitis were reported in the study. The two cases of endophthalmitis reported as ocular safety concerns in the study eye were classified by the MedDRA preferred term 'uveitis' (1 patient Group I; 1 patient in Group II).

Eleven (11) patients were reported to have experienced at least one non-ocular SAE during the course of the study (Group I, 6 [5.7%] patients; Group II, 5 [4.2%] patients; Group III, no patients), No non-ocular SAE occurred in more than 1 patient during the course of the study. None of the non-ocular SAEs were suspected to be related to study drug and/or ocular injection.

No AEs resulted in permanent treatment discontinuations during the course of the study. Treatment was interrupted temporarily due to AE or laboratory test abnormality in 4 patients in Group I and 2 patients in Group II.

8.9.1.7. Other safety matters

No clinically significant changes from baseline in clinical chemistry parameters were observed during the course of the study (that is, haematology, biochemistry and urinalysis). Changes in blood pressure observed in the study were transient and infrequent. Electrocardiograms were not reported during the study.

No clinically significant differences in ocular safety concerns in the study eye or in systemic safety concerns were observed between patients aged < 65 years and ≥ 65 years, or between male and female patients.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of ranibizumab administered by IVT injection for the treatment of impaired VA due to CNV secondary to PM have been satisfactorily demonstrated in the pivotal Phase III study (CRFB002F2301). In this study, both ranibizumab treatment groups (Group 1 ranibizumab/ stabilization; Group II ranibizumab/disease activity) demonstrated significantly greater improvements in mean average change in BCVA from Baseline to Month 1 through Month 3 compared with the vPDT treatment group (Group III). The mean average increase in BCVA score in the study eye was 10.5 letters in Group I (n=116), 10.6 letters in Group II (n=116), and 2.2 letters in Group III (n=55); confirmatory one-sided p≤ 0.001 for both pairwise comparisons (that is, Group I versus Group III, Group II versus Group III). The difference in the LSMs for the BCVA between ranibizumab (Group I) and vPDT (Group III) was 8.5 letters (95% CI: 5.8, 11.2),

and between ranibizumab (Group II) and vPDT (Group III) was 8.6 letters (95% CI: 6.1, 11.1). The difference in the LSMs for the BCVA (letters) in favour of ranibizumab compared with vPDT is considered to be clinically meaningful for both pairwise comparisons.

The mean average increase from Baseline from Month 1 through Month 6 in BCVA was similar in patients in Group I (ranibizumab/stabilization) and in Group II (ranibizumab/disease activity); 11.9 and 11.7 letters, respectively. The change in BCVA in Group II was statistically non-inferior compared with the change in BCVA in Group I, confirmatory one-sided $p<0.025$. The difference in the LSMs for the BCVA between Groups I and II of -0.1 letters (95% CI: -2.2, 2.0) is considered to be clinically insignificant.

The descriptive statistics for the multiple secondary and exploratory efficacy endpoint outcomes consistently favoured ranibizumab compared with vPDT, and showed that the differences between the two ranibizumab treatment groups (Group II/stabilization; Group II/disease activity) were unlikely to be clinically significant. In particular, the improvement in BCVA from baseline in both ranibizumab treatment groups was maintained from Month 3 through Month 12. The mean improvements in BCVA (letters) from baseline in Groups I, II and III were, respectively, 12.1 versus 12.5 versus 1.4 at Month 3, 13.7 versus 12.7 versus 7.9 at Month 6, and 13.8 versus 14.4 versus 9.3 at Month 12. The mean average increase in BCVA from Baseline to Month 1 through Month 12 was 12.8 letters in Group I (ranibizumab/stratified[10]), 12.5 letters in Group II (ranibizumab/disease activity), and 6.4 letters in Group III. In addition, the proportion of patients gaining ≥ 10 or ≥ 15 letters (or reaching a BCVA of ≥ 84 letters) from Baseline increased continuously throughout treatment in the three treatment groups and was notably higher in both Groups I and II than in Group III. In contrast, the proportion of patients losing ≥ 10 or ≥ 15 letters over the course of the study occurred infrequently in the three treatment groups.

The secondary efficacy endpoints assessing anatomical changes all supported ranibizumab in both Groups I and II (that is, change in CRT over time, change in CFT over time, proportion of patients with subretinal fluid, proportion of patients with intraretinal oedema, and proportion of patients with intraretinal cysts). Similarly, the exploratory endpoints relating to evaluation of change in CNV parameters, and change in patient reported outcomes all supported the efficacy of ranibizumab in both Groups I and II.

Overall, efficacy outcomes in Groups I and II were similar and the observed differences between the two groups are considered to be clinically insignificant. However, fewer ranibizumab injections were required by patients in Group II (re-treatment based on disease activity criteria), on average, than in Group I (re-treatment based on stabilization criteria). In Group I, the mean (SD) number of ranibizumab injections up to Month 3 was 2.5 (0.56) compared with 1.8 (0.82) in Group II. Therefore, from Baseline up to Month 3 there were, on average, 0.7 fewer injections in Group II compared with Group I, while the mean change in BCVA from Baseline through Month 3 was similar in both groups (Group I, 10.5 letters and Group II, 10.6 letters). The pattern of smaller mean number of injections in Group II compared with Group I was observed from Baseline up to Month 3 (1.8 versus 2.5, respectively), from Baseline up to Month 6 (2.5 versus 3.5, respectively), and from Baseline up to Month 12 (3.5 versus 4.6, respectively).

In Group I (FAS), 25.7% (27/105) of patients required 1 or 2 injections, 40.1% (43/105) of patients required 3 to 5 injections, and 33.3% (35/105) of patient required 6 to 12 injections up to Month 12. In Group II (FAS), 50.9% (59/116) of patients required 1 or 2 injections, 34.5% (40/166) required 3 to 5 injections, and 14.7% (17/116) required 6 to 12 injections up to Month 12.

Based on the fewer number of ranibizumab injections received by patients in Group II compared with Group I, and the similarity of efficacy outcomes in the two groups, it is

[10] Erratum: ranibizumab/stabilization

recommended that an individualized re-treatment regimen be approved consistent with that followed in Group II (that is, re-treatment based on disease activity criteria).

9.2. First round assessment of risks

The risks associated with ranibizumab for the treatment of visual impairment due to CNV secondary to PM are consistent with the known risks of the drug for the treatment of the approved indications of wet AMD, VA due to DME and VA due to macular oedema secondary to RVO. The risks described below are based on the safety data from the pivotal Phase III study (CRFB002F2301). In this study, the safety set included a total of 277 patients consisting of 106 patients in Group I (ranibizumab/stabilization), 118 patients in Group II (ranibizumab/disease activity), and 53 patients in Group III (vPDT).

Overall, total of 13 patients experienced at least 1 SAE during the 12-months of the study; 11 experienced non-ocular SAEs (6 [5.1%] patients in Group I and 5 [4.2%] patients in Group II), and 2 experienced ocular SAEs in the study eye (1 [0.9%] in Group I and 1 [0.8%] in Group II). The ocular SAEs in the study eye consisted of a corneal abrasion considered to be related to ocular injection in one patient in Group I, and retinoschisis unrelated to the study drug and/or ocular injection in one patient in Group II. None of the non-ocular SAEs were considered to be related to study drug and/or ocular injection, and none of the events were reported more than once.

No SAEs of endophthalmitis were reported in the study. However, endophthalmitis categorized as an ocular safety concern (RMP) in the study eye, but coded as 'uveitis' by MedDRA preferred term was reported in 2 patients (Group I, n=1; Group II, n=1). No AEs resulted in permanent treatment discontinuations during the course of the study. However, treatment was interrupted temporarily due to AE or laboratory test abnormality in 4 patients in Group I and 2 patients in Group II. No patients died during the 12 month study period. There were no deaths reported in the study.

The treatment-related risks observed with ranibizumab were most commonly ocular AEs in the study eye suspected to be related to ocular injection rather than study drug. Overall, the risks of ocular AEs in the study eye occurring in patients from Baseline up to Month 3 and suspected to be related to ocular injection were 17.9% (19/106) in Group I, 8.5% (10/118) in Group II, and 5.7% (3/53) in Group III (vPDT). The most frequently occurring ocular AEs in the study eye from Baseline up to Month 3 suspected to be related to ocular injection and reported in ≥ 1% of patients in any of the three treatment groups (Group I versus Group II versus Group III), respectively, were conjunctival haemorrhage (7.5%, n=8 versus 4.2%, n=5 versus 0%), punctate keratitis (2.8%, n=3 versus 1.7%, n=2 versus 3.8%, n=2), eye pain (1.9%, n=2 versus 0.8%, n=1 versus 0%), IOP increased (1.9%, n=2 versus 0.8%, n=1 versus 1.9%, n=1), and conjunctival hyperaemia (0% versus 0% versus n=1, 1.9%). There was only one ocular AE occurring from Baseline up to Month 3 suspected to be related to the study drug rather than ocular injection (vitreous floaters in 1, 0.8%, patient in Group II).

There was an association between the risk of ocular AEs in the study eye occurring from Baseline up to Month 3 suspected to be related to the ocular injection and the number of ranibizumab injections given in this time period. The mean number of ranibizumab injections administered to patients in Groups I, II, and III from Baseline to Month 3 was 2.5 (range: 1-3), 1.8 (range: 1-3), and 0 (range: 0 to 0), respectively.

From Baseline up to Month 12, ocular AEs in the study eye suspected to be related to ocular injection were reported in 24.5% (26/106) of patients in Group I and 20.3% (24/118) of patients in Group II. The most frequently occurring ocular AEs in the study eye from Baseline up to Month 12 suspected to be related to ocular injection and reported in ≥ 1% of patients in Group I or Group II, respectively, were conjunctival haemorrhage (9.4%, n=10 versus 8.5%, n=10), punctate keratitis (4.7%, n=5 versus 1.7%, n=2), eye pain (2.8%, n=3 versus 2.5%, n=3), injection site haemorrhage (2.8%, n=3 versus 2.8%, n=3), and IOP increased (2.8%, n=3 versus

4.2%, n=5). From Baseline up to Month 12, ocular AEs in the study eye suspected to be related to study drug rather than to ocular injection were reported in 2 (1.9%) patients in Group I (2 events - eye pain and IOP increased), and 2 (1.7%) patients in Group II (4 events - eye irritation, metamorphopsia, ocular hyperaemia, and vitreous floaters).

There was an association between the risk of ocular AEs in the study eye from Baseline up to Month 12 suspected to be related to the ocular injection and the number of ranibizumab injections given in this time period. The mean number of ranibizumab injections administered in Group I and Group II from Baseline to Month 12 was 4.6 (range: 1-11) and 3.5 (range: 1-12), respectively.

From Month 3 to Month 12, ocular AEs in the study eye suspected to be related to ocular injection were reported in 18.4% (7/38) of patients in Group III with ranibizumab and 13.3% (2/15) of patients in Group III without ranibizumab. Ocular AEs in the study eye from Month 3 to Month 12 suspected to be related to ocular injection and reported in ≥ 2 patients in either Group III with ranibizumab or Group III without ranibizumab, respectively, were conjunctival haemorrhage (5.3%, n=2 versus 0%), punctate keratitis (5.3%, n=2 versus 0%), injection site haemorrhage (5.3%, n=2 versus 0%), and IOP increased (5.3%, n=2 versus 0%). In Group III (vPDT with ranibizumab), the mean number of ranibizumab injections up to Month 12 was 3.5 (range: 1-9). From Month 3 to Month 12, ocular AEs in the study eye suspected to be related to study drug rather than to ocular injection were reported in 2 (5.3%) patients in Group III with ranibizumab (3 events - 2x visual impairment, 1x ocular hyperaemia), and no patients in Group III without ranibizumab.

While the risks of non-ocular AEs regardless of the relationship to treatment were commonly reported with ranibizumab, the risks of non-ocular AEs considered to be related to the study drug and/or ocular injection in patients treated with ranibizumab were small. Non-ocular AEs regardless of relationship to treatment occurring from Baseline up to Month 3 were reported in 25.5% (27/106) of patients in Group I, 25.4% (30/118) of patients in Group II, and 11.3% (6/53) in Group III. Non-ocular AEs suspected to be related to study drug/and or ocular injection from Baseline up to Month 3 were reported in no patients in Groups I and III, and 2 (1.7%) patients in Group II (2 events – headache, nausea). Non-ocular AEs regardless of relationship to treatment occurring from Baseline up to Month 12 were reported in 45.3% (48/106) of patients in Group I and 43.2% (51/118) of patients in Group II. Non-ocular AEs suspected to be related to study drug/and or ocular injection from Baseline up to Month 12 were reported in no patients in Group I and 3 (2.5%) patients in Group II (3 events – headache, hepatic function abnormal, nausea). Non-ocular AEs regardless of relationship to treatment from Month 3 to Month 12 were reported in 50.0% (19/38) of patients in Group III with ranibizumab and 33.3% (5/15) of patients in Group III without ranibizumab. Non-ocular AEs suspected to be related to study drug/and or ocular injection from Month 3 to Month 12 were reported in no patients in Group III with or without ranibizumab.

The risk of ocular safety concerns (RMP) in the study eye occurring from Baseline up to Month 3 in patients in the three treatment groups were: Group I – endophthalmitis (n=1, 0.9%)[11], cataract (n=1, 0.9%), transient IOP increased (n=2, 1.9%), and retinal tear (n=1, 0.9%); Group II – transient IOP increased (n=2, 1.7%); and Group III – intraocular inflammation (n=1, 1.9%), and transient IOP increased (n=1, 1.9%). From Baseline up to Month 3, none of the patients in the three treatment groups were reported to have experienced ocular safety concerns in the study eye of deterioration of retinal blood flow, retinal detachment, retinal pigment epithelial tear, vitreous haemorrhage, or glaucoma.

The risk of ocular safety concerns (RMP) in the study eye from Baseline up to Month 12 in patients in Group I were endophthalmitis (n=1, 0.9%), intraocular inflammation (n=1, 0.9%), cataract (n=3, 2.8%), transient IOP increased (n=3, 2.8%), and retinal tear (n=2, 1.9%), and in

[11] Erratum: endophthalmitis category (PT uveitis: 1, 0.9%)

patients in Group II were endophthalmitis (n=1, 0.8%), intraocular inflammation (n=4, 3.4%), cataract (n=2, 1.7%), transient IOP increased (n=7, 5.9%), retinal tear (n=1, 0.8%), and glaucoma (n=1, 0.8%). From Baseline up to Month 12, there had been no reports of ocular safety concerns in the study eye of deterioration of retinal blood flow, retinal detachment, retinal pigment epithelial tear, or vitreous haemorrhage in patients in Groups I or II. The risk of ocular safety concerns (RMP) in the study eye from Month 3 up to Month 12 in patients in Group III with ranibizumab were intraocular inflammation (n=2, 5.3%), cataract (n=1, 2.6%), transient IOP increased (n=4, 10.5%), and glaucoma (n=1, 2.6%), and in patients in Group III without ranibizumab were cataract (n=1, 6.7%).

The risks of systemic AEs of special concern occurring from Baseline up to Month 3 in patients in the three treatment groups were: Group 1 – hypersensitivity (n=3, 2.8%) and hypertension (n=1, 0.9%); Group II – hypersensitivity (n=2, 1.7%), hypertension (n=3, 2.5%), and non-ocular haemorrhage (n=2, 1.7%); and Group III – hypertension (n=1, 1.9%). There were no reports of systemic AEs of special concern of proteinuria, myocardial infarction, other arterial thromboembolic events, or venous thromboembolic events from Baseline to Month 3.

The risks of systemic safety concerns (RMP) from Baseline up to Month 12 in patients in Group I were hypersensitivity (n=8, 7.5%), hypertension (n=4, 3.8%), non-ocular haemorrhage (n=2, 1.9%) and other arterial thromboembolic events (n=1, 0.9%), and in Group II were hypersensitivity (n=9, 7.6%), hypertension (n=5, 4.2%) and non-ocular haemorrhage (n=5, 4.2%). Systemic safety concerns (RMP) occurring from Month 3 to Month 12 in patients in Group III with ranibizumab were hypersensitivity (n=2, 5.3%) and hypertension (n=3, 7.9%), while no systemic AEs of special concern were reported in Group III without ranibizumab. In Groups I and II, there had been no reports of systemic AEs of special concern of proteinuria, myocardial infarction, or venous thromboembolic events from Baseline to Month 12. In Group III, with and without ranibizumab, there had been no reports of systemic AEs of special concern of non-ocular haemorrhage, proteinuria, myocardial infarction, other thromboembolic events, or venous thromboembolic events from Month 3 to Month 12.

There appear to be no clinically significant risks of laboratory abnormalities (haematology, biochemistry, urinalysis) or changes in vital signs (blood pressure, pulse rate) occurring in patients with visual impairment due to CNV secondary to PM.

9.3. First round benefit-risk assessment

Overall, the benefit-risk assessment of ranibizumab, given the proposed usage is favourable.

The favourable benefit-risk assessment is based on the Group II treatment regimen. In this group, patients received an initial IVT injection of ranibizumab 0.5 mg, and further injections were given at monthly intervals only when disease activity criteria were observed. Therefore, in this group the number of injections based on disease activity could range from 1 to 12. In Group II (FAS), 50.9% of patients required 1 or 2 injections, 34.5% required 3 to 5 injections, and 14.7% required 6 to 12 injections up to Month 12.

The sponsor is proposing a treatment regimen based on that followed in Group II (that is, re-treatment driven by disease activity), but with the frequency of monitoring as determined by the treating physician. However, monitoring in Group II was at monthly intervals for the first 12 months with the need for monthly re-treatment being determined by assessment of specified re-treatment criteria. Consequently, it is reasonable to conclude that monitoring should be at monthly intervals for at least the first 12 months in order to assess the need for re-treatment at each monthly visit.

It is noted that the proposed EU prescribing information recommends monthly monitoring for the first two months and at least every three months thereafter during the first year, after which the frequency of monitoring should be determined by the treating physician. The EU re-treatment monitoring regimen is a compromise between the frequency of monitoring after the

first injection being determined by the treating physician proposed by the sponsor, and the monthly monitoring regimen followed in Group II in the pivotal Phase III study. It is considered that, as the benefit-risk assessment is based on that followed in Group II, then monitoring should be at monthly intervals in the first 12 months of treatment after which monitoring should be determined by the treating physician. However, it is noted that data from the pivotal Phase III study showed that the majority of patients assessed at each month for the first 12 Months did not require re-treatment with ranibizumab based on disease activity criteria. For example, in the safety set the percentage of patients re-treated at Months 1, 2, 5, 8 and 11 in Group II based on assessment of disease activity (irrespective of disease stability) was 45.8%, 34.7%, 16.9%, 17.0%, and 13.4%, respectively.

The benefits of ranibizumab in the proposed patient population include clinically meaningful improvement in BCVA from baseline and improvements in retinal abnormalities including CRT, CFT, subretinal fluid, intraretinal oedema, and intraretinal cysts. In addition, exploratory data suggest that ranibizumab improves patient reported quality of life outcomes. The benefits associated with ranibizumab were similar for treatment based on disease stabilization criteria and disease activity. However, patients in the ranibizumab by disease activity criteria group required, on average, approximately one less injection over the 12 month treatment period than patients in the ranibizumab by disease stabilization group.

The risks of treatment with ranibizumab for the proposed indication are consistent with the known risks of treatment with ranibizumab for the approved indications. The risks of ocular AEs in the study eye from treatment with ranibizumab appear to be primarily related to ocular injection rather than study drug. From Baseline up to Month 3, the risks of ocular AEs in the study eye were greater in patients in the ranibizumab by stabilization group than in the ranibizumab by disease activity group, and the risks in both ranibizumab groups were greater than the risks in the vPDT group. From Baseline up to Month 12, the risks of ocular AEs in the study eye were greater in patients in the ranibizumab by stabilization group (Group 1) than in the ranibizumab by disease activity criteria group (Group II), and from Month 3 up to Month 12 the risks were greater in patients in Group III with treated with ranibizumab compared with patients in Group III treated without ranibizumab.

There are no risk-benefit data on patients with VA due to CNV secondary to PM treated with ranibizumab for more than 12 months. The information on risk-benefit of ranibizumab in patients with extrafoveal CNV is limited as only 4% (11/277) of patients in the pivotal Phase III study had visual impairment due to extrafoveal CNV lesions secondary to PM. The sponsor comments that although this proportion of patients is low it reflects the proportion of myopic patients with extrafoveal lesions in the general population. There is no risk-benefit information in children and adolescents (that is, patients aged ≤ 18 years) for the proposed indication. However, the sponsor comments that visual impairment due to CNV secondary to PM is not prevalent. There is no risk-benefit information on patients with bilateral use of ranibizumab for the treatment of patients with the proposed indication.

10. First round recommendation regarding authorisation

It is recommended that ranibizumab be approved for the treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathological myopia (PM).

11. Clinical questions

11.1. Pharmacokinetics

Nil.

11.2. Pharmacodynamics

Nil.

11.3. Efficacy

1. In the CSR for CRFB002F2301, the proportion of patients (FAS/LOCF) with definite subretinal fluid (volume scan) for the three treatment groups at Months 3, 6, and 12 presented in Table 11-15 differs from that in PT-Table 14.2-3.8 (which is identified as the source for the data in Table 11-15). Please account for this apparent discrepancy.
2. In the CSR for CRFB003F2301, the proportion of patients (FAS/LOCF) with definite intraretinal oedema (volume scan) in patients at Month 3 in Group II and Group III presented in Table 11-16 differs from that in PT-Table 14.2-3.12 (which is identified as the source for the data in Table 11-16). Please account for this apparent discrepancy.
3. In the CSR for CRFB002F2301, the proportion of patients (FAS/LOCF) with definite intraretinal cysts (volume scan) for the three treatment groups at Months 3, 6, and 12 presented in Table 11-17 differs from that in PT-Table 14.2-3.16 (which is identified as the source for the data in Table 11-17). Please account for this apparent discrepancy.

11.4. Safety

4. Were the ocular AEs described in the Phase II ('supportive') study CRFB002AGBI0 for the study eye only or for the study eye plus the fellow eye?

12. Second round evaluation of clinical data submitted in response to questions

The sponsor has provided complete responses to the clinical questions raised following the first round evaluation of the submission. In the following sections, the questions raised in Section 10 of the CER have been repeated and the sponsor's responses to these questions have been provided in full. Clinical comments on the responses have been prepared based on evaluation data (CD) provided by the sponsor response dated 23 December 2013.

12.1. Efficacy - Clinical questions

12.1.1. Question 1

In the CSR for CRFB002F2301, the proportion of patients (FAS/LOCF) with definite subretinal fluid (volume scan) for the three treatment groups at Months 3, 6, and 12 presented in Table 11-15 differs from that in PT-Table 14.2-3.8 (which is identified as the source for the data in Table 11-15). Please account for this apparent discrepancy.

12.1.1.1. Sponsor's response

The post-text tables have a different format than the associated in-text tables. While the in-text table presents the number (%) of patients with their status with respect to subretinal fluid at specific visits (Baseline, Month 3, 6, 12) the post-text table presents the same data in a shift-table. The post-text shift table details the patients' status at baseline and - conditional on the baseline status - the shift table shows the status at the specific visits. For instance, the shift tables provide the number of patients at Month 6 with 'presence' of subretinal fluid, given the subgroup of patients at baseline with 'presence' of subretinal fluid.

The information presented in the in-text table is contained in the post-text shift table:

- The outcome at baseline in the in-text table matches the outcome in the associated post-text table.
- The outcome at Month 3, 6, 12 in the in-text table matches the outcome in the associated post-text table in the 'Total' row for each treatment group at the Month 3, 6, 12 visits.

12.1.1.2. Clinical evauator's comment

The sponsor's response is satisfactory. The data relating to the number of patients with subretinal fluid (volume scan) over time are presented in below in Table 22.

Table 22. Number (%) of patients with subretinal fluid volume (volume scan) of the study eye over time; FAS (LOCF).

Parameter Treatment	Category	Baseline n (%)	Month 3 n (%)	Month 6 n (%)	Month 12 n (%)
Subretinal fluid - overall					
Ranibizumab 0.5 mg Group I	Definite	37 (35.2)	7 (6.7)	6 (5.7)	7 (6.7)
	Absent	61 (58.1)	91 (86.7)	93 (88.6)	93 (88.6)
	Other	7 (6.7)	7 (6.7)	6 (5.7)	5 (4.8)
	Total	105 (100.0)	105 (100.0)	105 (100.0)	105 (100.0)
Ranibizumab 0.5 mg Group II	Definite	47 (40.5)	5 (4.3)	8 (6.9)	6 (5.2)
	Absent	60 (51.7)	103 (88.8)	102 (87.9)	104 (89.7)
	Other	9 (7.8)	8 (6.9)	6 (5.2)	6 (5.2)
	Total	116 (100.0)	116 (100.0)	116 (100.0)	116 (100.0)
vPDT Group III	Definite	19 (34.5)	13 (23.6)	1 (1.8)	2 (3.6)
	Absent	35 (63.6)	39 (70.9)	52 (94.5)	53 (96.4)
	Other	1 (1.8)	3 (5.5)	2 (3.6)	0
	Total	55 (100.0)	55 (100.0)	55 (100.0)	55 (100.0)

Source: CSR, Table 11-15. The category 'Other' includes 'Can't grade', 'Not applicable', and 'Missing'.
* Note: The majority of patients with no center involvement at Month 3, 6 and 12 were recorded as 'Not applicable'.

The shift data relating to patients with definite or absent subretinal fluid (volume scan) at baseline are presented in below in Table 23. The 'total' number of patients at each of the time points consists of patients with 'definite' or 'absent' subretinal fluid plus 'other' patients (that is, 'can't grade', 'not applicable', 'missing').

Table 23. Subretinal fluid (volume scan) of the study eye shift table from baseline to scheduled post-baseline visit for patients (n (%) with definite or absent subretinal fluid at baseline; FAS (LOCF).

Treatment	Baseline		Month 3		Month 6		Month 12	
			Definite	Absent	Definite	Absent	Definite	Absent
R 0.5 mg	D	37 (35.2)	6 (5.7)	31 (29.5)	5 (4.8)	31 (29.5)	4 (3.8)	32 (30.5)
GI (n=105)	A	61 (58.1)	1 (1.0)	56 (53.5)	1 (1.0)	58 (55.2)	3 (2.9)	56 (53.5)
		Total	7 (6.7%)	91 (86.7%)	6 (5.7)	93 (88.6)	7 (6.7)	93 (88.6)
R 0.5 mg	D	47 (40.5)	4 (3.4)	42 (36.2)	7 (6.0)	39 (33.6)	5 (4.3)	41 (35.3)
GII (n=116)	A	60 (51.7)	0	57 (49.1)	0	58 (50.0)	1 (0.9)	58 (50.0)
		Total	5 (4.3)	103 (88.8)	8 (6.9)	102 (87.9)	6 (5.2)	104 (89.7)
vPDT	D	19 (34.5)	9 (16.4)	9 (16.4)	0	19 (34.5)	1 (1.8)	18 (32.7)
GII (n=55)	A	35 (63.6)	4 (7.3)	29 (52.7)	1 (1.8)	32 (58.2)	1 (1.8)	34 (61.8)
		Total	13 (23.6)	39 (70.9)	1 (1.8)	52 (94.5)	2 (3.6)	53 (96.4)

Source: CSR, Adapted from Table 14.2-3.8. D=definite; A=absent, R = Ranibizumab; G = Group; vPDT = Visudyne photodynamic therapy. Note: Percentages are based on the total number of patients at baseline. The table excludes data for patients for whom subretinal fluid volume was not judged to be definite or absent at baseline (that is, questionable) and data for patients for whom subretinal fluid volume post-baseline was not judged to be definite or absent (that is, cannot grade, not applicable, or missing).

12.1.2. Question 2

In the CSR for CRFB003F2301, the proportion of patients (FAS/LOCF) with definite intraretinal oedema (volume scan) in patients at Month 3 in Group II and Group III presented in Table 11-16 differs from that in PT-Table 14.2-3.12 (which is identified as the source for the data in Table 11-16). Please account for this apparent discrepancy.

12.1.2.1. Sponsor's response

Please refer to the response to Question 1.

12.1.2.2. Clinical evaluator's comment

The sponsor's response is satisfactory. The data relating to the number of patients with intraretinal oedema over time are presented below in Table 24.

Table 24. Number (%) of patients with intraretinal oedema (volume scan) of the study eye over time; FAS (LOCF)

Parameter Treatment	Category	Baseline n (%)	Month 3 n (%)	Month 6 n (%)	Month 12 n (%)
Intraretinal edema - overall					
Ranibizumab 0.5 mg Group I	Definite	89 (84.8)	36 (34.3)	17 (16.2)	3 (2.9)
	Absent	11 (10.5)	62 (59.0)	82 (78.1)	97 (92.4
	Other	5 (4.8)	7 (6.7)	6 (5.7)	5 (4.8)
	Total	105 (100.0)	105 (100.0)	105 (100.0)	105 (100.0)
Ranibizumab 0.5 mg Group II	Definite	92 (79.3)	42 (36.2)	19 (16.4)	5 (4.3)
	Absent	17 (14.7)	66 (56.9)	92 (79.3)	106 (91.4)
	Other	7 (6.0)	8 (6.9)	5 (4.3)	5 (4.3)
	Total	116 (100.0)	116 (100.0)	116 (100.0)	116 (100.0)
vPDT Group III	Definite	48 (87.3)	31 (56.4)	8 (14.5)	1 (1.8)
	Absent	7 (12.7)	21 (38.2)	44 (80.0)	54 (98.2)
	Other	0	3 (5.5)	3 (5.5)	0
	Total	55 (100.0)	55 (100.0)	55 (100.0)	55 (100.0)

Source: CSR, Table 11-16. The category 'Other' includes 'Can't grade', 'Not applicable', and 'Missing'. * Note: The majority of patients with no center involvement at Month 3, 6 and 12 were recorded as 'Not applicable'.

The shift data relating to patients with definite or absent intraretinal oedema (volume scan) at baseline are presented below in Table 25. The 'total' number of patients at each of the time points consists of patients with 'definite' or 'absent' intraretinal oedema plus 'other' patients (that is, 'can't grade', 'not applicable', 'missing').

Table 25. Intraretinal oedema (volume scan) of the study eye shift table from baseline to scheduled post-baseline visit for patients (n (%) with definite or absent subretinal fluid at baseline; FAS (LOCF).

Treatment	Baseline		Month 3		Month 6		Month 12	
			Definite	Absent	Definite	Absent	Definite	Absent
R 0.5 mg	Definite	89 (84.8)	36 (34.3)	52 (49.5)	17 (16.2)	71 (67.6)	3 (2.9)	84 (80.0)
GI (n=105)	Absent	11 (10.5)	0	9 (8.6)	0	9 (8.6)	0	10 (9.5)
		Total	36 (34.3)	62 (59.0)	17 (16.2)	82 (78.1)	3 (2.9)	97 (92.4)
R 0.5 mg	Definite	92 (79.3)	40 (34.5)	48 (41.4)	19 (16.4)	71 (61.2)	5 (4.3)	86 (74.1)
GII (n=116)	Absent	17 (14.7)	0	15 (12.9)	0	17 (14.7)	0	17 (14.7)
		Total	42 (36.2)	66 (56.9)	19 (16.4)	92 (79.3)	5 (4.3)	106 (91.4)
vPDT	Definite	48 (87.3)	30 (54.4)	15 (27.3)	8 (14.4)	37 (67.3)	1 (1.8)	47 (85.5)
GII (n=55)	Absent	7 (12.7)	1 (1.8)	6 (10.9)	0	7 (12.7)	0	7 (12.7)
		Total	31 (56.4)	21 (38.2)	8 (14.5)	44 (88.0)	1 (1.8)	54 (98.2)

Source: CSR, Adapted from Table 14.2-3.12. R = Ranibizumab; G = Group; vPDT = Visudyne photodynamic therapy. Note: Percentages are based on the total number of patients at baseline. The table excludes data for patients for whom intraretinal oedema was not judged to be definite or absent at baseline (that is, questionable) and data for patients for whom intraretinal oedema post-baseline was not judged to be definite or absent (that is, cannot grade, not applicable, or missing).

12.1.3. Question 3

In the CSR for CRFB002F2301, the proportion of patients (FAS/LOCF) with definite intraretinal cysts (volume scan) for the three treatment groups at Months 3, 6, and 12 presented in Table 11-17 differs from that in PT-Table 14.2-3.16 (which is identified as the source for the data in Table 11-17). Please account for this apparent discrepancy.

12.1.3.1. Sponsor's response

Please refer to the response to Question 1.

12.1.3.2. Clinical evaluator's comment

The sponsor's response is satisfactory. The data relating to the number of patients with intraretinal cysts (volume scan) over time are presented below in Table 26.

Table 26. (%) of patients with intraretinal cysts (volume scan) of the study eye over time; FAS (LOCF)

Parameter Treatment	Category	Baseline n (%)	Month 3 n (%)	Month 6 n (%)	Month 12 n (%)
Intraretinal cysts - overall					
Ranibizumab 0.5 mg Group I	Definite	29 (27.6)	19 (18.1)	18 (17.1)	14 (13.3)
	Absent	68 (64.8)	77 (73.3)	82 (78.1)	86 (81.9)
	Other	8 (7.6)	9 (8.6)	5 (4.8)	5 (4.8)
	Total	105 (100.0)	105 (100.0)	105 (100.0)	105 (100.0)
Ranibizumab 0.5 mg Group II	Definite	32 (27.6)	27 (23.3)	11 (9.5)	13 (11.2)
	Absent	73 (62.9)	79 (68.1)	99 (85.3)	97 (83.6)
	Other	11 (9.5)	10 (8.6)	6 (5.2)	6 (5.2)
	Total	116 (100.0)	116 (100.0)	116 (100.0)	116 (100.0)
vPDT Group III	Definite	10 (18.2)	13 (23.6)	6 (10.9)	12 (21.8)
	Absent	40 (72.7)	39 (70.9)	46 (83.6)	43 (78.2)
	Other	5 (9.1)	3 (5.5)	3 (5.5)	0
	Total	55 (100.0)	55 (100.0)	55 (100.0)	55 (100.0)

Source: CSR, Table 11-17. The category 'Other' includes 'Can't grade', 'Not applicable', and 'Missing'.
* Note: The majority of patients with no center involvement at Month 3, 6 and 12 were recorded as 'Not applicable'.

The shift data relating to patients with definite or absent intraretinal cysts (volume scan) at baseline are presented below in Table 27. The 'total' number of patients at each of the time points consists of patients with 'definite' or 'absent' intraretinal cysts plus 'other' patients (that is, 'can't grade', 'not applicable', 'missing').

Table 27. Intraretinal cysts (volume scan) of the study eye shift table from baseline to scheduled post-baseline visit for patients (n (%) with definite or absent subretinal fluid at baseline; FAS (LOCF).

Treatment	Baseline		Month 3		Month 6		Month 12	
			Definite	Absent	Definite	Absent	Definite	Absent
R 0.5 mg	Definite	29 (27.6)	15 (14.3)	13 (12.4)	13 (12.4)	16 (15.2)	11 (10.5)	17 (16.2)
GI (n=105)	Absent	68 (64.8)	4 (3.8)	60 (57.1)	5 (4.8)	61 (58.1)	3 (2.9)	63 (60.0)
		Total	19 (18.1)	77 (73.3)	18 (17.1)	82 (78.1)	14 (13.3)	86 (81.9)
R 0.5 mg	Definite	32 (27.6)	17 (14.7)	13 (11.2)	8 (6.9)	22 (19.0)	10 (8.6)	22 (19.0)
GII (n=116)	Absent	73 (62.9)	10 (8.6)	59 (50.9)	3 (2.6)	69 (59.5)	3 (2.6)	69 (59.5)
		Total	27 (23.3)	79 (68.1)	11 (9.5)	99 (85.3)	13 (11.2)	97 (83.6)
vPDT	Definite	10 (18.2)	5 (9.1)	5 (9.1)	3 (5.5)	7 (12.7)	3 (5.5)	7 (12.7)
GII (n=55)	Absent	40 (72.7)	7 (12.7)	31 (56.4)	2 (3.6)	36 (65.5)	9 (16.4)	31 (56.4)
		Total	13 (23.6)	39 (70.9)	6 (10.9)	46 (83.6)	12 (21.8)	43 (78.2)

Source: CSR, Adapted from Table 14.2-3.16. R = Ranibizumab; G = Group; vPDT = Visudyne photodynamic therapy. Note: Percentages are based on the total number of patients at baseline. The table excludes data for patients for whom intraretinal cyst was not judged to be definite or absent at baseline (that is, questionable)

and data for patients for whom intraretinal cysts post-baseline was not judged to be definite or absent (that is, cannot grade, not applicable, or missing).

12.2. Safety - Clinical questions

12.2.1. Question 1

Were the ocular AEs described in the Phase II ('supportive') study CRFB002AGBI0 for the study eye only or for the study eye plus the fellow eye?

12.2.1.1. Sponsor's response

All reported ocular AEs in the study CRFB002AGBI0 are from both eyes (study eye plus fellow eye).

12.2.1.2. Clinical evaluator's comment

The response is satisfactory.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

The benefits of ranibizumab, given the proposed usage are favourable. The second round assessment of the benefits of treatment remains unchanged from the first round assessment. The benefits of ranibizumab administered by IVT injection for the treatment of impaired VA due to CNV secondary to PM have been satisfactorily demonstrated in the pivotal Phase III study (CRFB002F2301).

In CRFB002F2301, both ranibizumab treatment groups (Group 1 re-treatment based on stabilization and Group II re-treatment based on disease activity) demonstrated significantly greater improvements in mean average change in BCVA from Baseline to Month 1 through Month 3 (primary efficacy outcome) compared with the vPDT treatment group (Group III). The mean average increase in BCVA score in the study eye was 10.5 letters in Group I, 10.6 letters in Group II, and 2.2 letters in Group III; confirmatory one-sided $p \leq 0.001$ for both pairwise comparisons (that is, Group I versus Group III, Group II versus Group III). The difference in the LSMs for the BCVA between ranibizumab (Group I) and vPDT (Group III) was 8.5 letters (95% CI: 5.8, 11.2), and between ranibizumab (Group II) and vPDT (Group III) was 8.6 letters (95% CI: 6.1, 11.1). The difference in the LSMs for the BCVA (letters) in favour of ranibizumab compared with vPDT is considered to be clinically meaningful for both pairwise comparisons.

In CRFB002F2301, the mean average change from baseline from Month 1 to Month 6 in BCVA (key secondary efficacy endpoint) was similar in patients treated with ranibizumab in Group 1 and Group II (11.9 and 11.7 letters, respectively), and the improvement from baseline was statistically significant in both Groups (nominal one-sided $p < 0.00001$). The mean average change in Group I was statistically non-inferior compared with Group II (that is, one-sided $p < 0.025$, adjusted for multiplicity of testing of primary and key secondary efficacy outcomes). The difference in the LSM for the BCVA between Group I and II of -0.1 (95% CI: -2.2, 2.0) letters is considered to be clinically insignificant.

In CRFB002F2301, fewer ranibizumab injections were required by patients in Group II than in Group I. In Group I (FAS), 25.7% of patients required 1 or 2 injections, 40.1% of patients required 3 to 5 injections, and 33.3% of patient required 6 to 12 injections up to Month 12. In Group II (FAS), 50.9% of patients required 1 or 2 injections, 34.5% required 3 to 5 injections, and 14.7% required 6 to 12 injections up to Month 12. In Group I, 62.9% of patients did not required a ranibizumab injection within the period from Month 6 to end of study, compared with 50.5% of patients in Group II.

Based on the fewer number of ranibizumab injections received by patients in Group II compared with Group I, and the similarity of efficacy outcomes in the two groups, it is recommended that re-treatment be based on disease activity criteria.

13.2. Second round assessment of risks

The risks of ranibizumab, given the proposed usage are favourable. The second round assessment of the risks of treatment remains unchanged from the first round assessment. The risks associated with ranibizumab for the treatment of visual impairment due to CNV secondary to PM are consistent with the known risks of the drug for the treatment of the approved indications of wet AMD, VA due to DME and VA due to macular oedema secondary to RVO.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of ranibizumab, given the proposed usage is favourable. After consideration of the sponsor's response relating to the frequency of monitoring it is recommended that the monitoring regimen proposed by the sponsor be approved.

Monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year of treatment. After the first year of year of treatment, the frequency of monitoring should be determined by the treating physician. It is unlikely that the benefit-risk balance for ranibizumab for the proposed usage based on the proposed monitoring regimen will differ significantly from a monitoring regimen based on monthly assessment for the first year, followed thereafter by physician determined monitoring.

14. Second round recommendation regarding authorisation

It is recommended that ranibizumab be approved for the treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathological myopia (PM).

15. References

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