



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Ranibizumab

Proprietary Product Name: Lucentis

Sponsor: Novartis Pharmaceuticals Australia Pty
Ltd

October 2014

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List of the most common abbreviations used in this AusPAR

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
CNV	Choroidal Neovascularization
CRT	Central Retinal Thickness
CRVO	Central Retinal Vein Occlusion
CSR	Clinical Study Report
D	Diopetre
DME	Diabetic Macular Edemae
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
IVT	Intravitreal
LSM	Least squares mean

Abbreviation	Meaning
MedDRA	Medical Dictionary for Regulatory Activities
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

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	28 April 2014
<i>Active ingredient:</i>	Ranibizumab – recombinant, humanised, monoclonal antibody fragment against vascular endothelial growth factor (anti-VEGF).
<i>Product name:</i>	Lucentis
<i>Sponsor's name and address:</i>	Novartis Pharmaceuticals Australia PO Box 101 North Ryde NSW 1670
<i>Dose form:</i>	Solution for injection
<i>Strengths:</i>	1.65 µg/0.165 mL and 2.3 mg/0.23 mL ¹
<i>Containers:</i>	Pre-filled syringe or glass vial with needle.
<i>Pack sizes:</i>	One pre-filled syringe or a single glass vial.
<i>Approved therapeutic use:</i>	<i>Lucentis (ranibizumab) is indicated in adults for the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).</i>
<i>Route of administration:</i>	Intravitreal injection (IVT)
<i>Dosage:</i>	Dosage is dependent on the condition being treated (see Product Information Attachment 1 for details).
<i>ARTG numbers:</i>	148325 and 212387

Product background

This AusPAR describes the application by the sponsor to extend the indications for Lucentis (ranibizumab) in the treatment of impaired visual acuity (VA) due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM) to include following indication:

Treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).

The currently approved indications for Lucentis in Australia are:

¹ Following the Clinical Delegate's advice in the email correspondence of 25 February 2014 that the instruction to use 0.05 mL to inject 0.5 mg dose (that is, the dosage required for the proposed indication) is not correct for Lucentis ranibizumab (rbe) 1.8 mg/0.3 mL solution for injection (AUST R 125968) strength, the sponsor withdrew this presentation from the submission and requested in their email correspondence of 26 February 2014 that the Lucentis ranibizumab (rbe) 1.65 mg/0.165 mL solution for injection prefilled syringe (AUST R 212387) be included instead in this submission. Hence, the application was at this stage altered to be for the 2.3 mg/0.23 mL and 1.65/0.165 mL strengths and not to include the 1.8 mg/0.3 mL strength.

- *Treatment of neovascular (wet) age-related macular degeneration (AMD).*
- *Treatment of visual impairment due to diabetic macular oedema (DME).*
- *Treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).*

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (for example, VEGF₁₁₀, VEGF₁₂₁ and VEGF₁₆₅), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration or pathologic myopia and the macular oedema causing visual impairment in diabetes and retinal vein occlusion.

Verteporfin (Visudyne) photodynamic therapy (vPDT) is currently approved in Australia for the treatment of patients with subfoveal choroidal neovascularisation due to age-related macular degeneration or patients with subfoveal choroidal neovascularisation caused by 'other' macular diseases. This may be considered as applying to myopia indication. A clinical trial of vPDT in PM is described in the approved Visudyne PI.

The sponsor's current submission was based on clinical and risk management plan (RMP) dossiers only. There were no quality or nonclinical data submitted.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 28 October 2008.

At the time the TGA considered this application, similar applications had been approved in the European Union (EU), Switzerland and Canada (see Table 1 below) and was under consideration in New Zealand.

Table 1. International regulatory status

Country/ Region	Tradename	Submitted	Approved	Approved Indication
EU	LUCENTIS	September 2012	4 July 2013	The treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM)
Canada	LUCENTIS	June 2013	28 January 2014	The treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM)
New Zealand	LUCENTIS	October 2013	TBA	The treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM)
Switzerland	LUCENTIS	February 2013	14 August 2013	The treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM)

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

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, e.g. 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 to 21%) compared with Caucasian populations (2 to 4%).² 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 to 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.² The disease occurs more commonly in females compared with males (estimated 67% versus 33%, respectively).² More than 50% of CNV affected PM patients have a presenting age

² Chan W-M *et al.* Choroidal neovascularisation in pathological myopia: an update in management. *Br J Ophthalmol* 2005;89:1522-1528.

of 50 years or less², and the condition has a poor prognosis with a significant risk of visual deterioration.³

Guidance

See *Guidelines for submissions supported by only one pivotal study* below.

Contents of the clinical dossier

The submission included the following clinical information:

- 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 sponsor's Summary of Clinical Efficacy and the Summary of Clinical Safety.
- Lucentis Core Data Sheet (CDS), Version 1.2; statement on case report forms and individual listings for clinical trials.
- Literature References.

Paediatric data

The sponsor stated that, based on a product specific waiver granted by the EMA on 22 December 2010, 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'*.

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.

Pharmacokinetics

There were no new data submitted.

Pharmacodynamics

There were no new data submitted.

Dosage selection for the pivotal studies

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

³ Pece A *et al.* Management of choroidal neovascularisation in myopic macular degeneration. Expert Review of Ophthalmology 2008;3:311-323.

Efficacy

Studies providing efficacy data

The following two studies were submitted:

- A Phase III clinical efficacy and safety study (RFB002F2301).
- A Phase II clinical efficacy and safety study (CRFB002AGB10), considered by the TGA to be supportive.

Evaluator's conclusions on efficacy

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.

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 Best-corrected visual acuity (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 Optical Coherence Tomography (OCT) and/or Fluorescein Angiography/Angiogram (FA)).

In Group III, patients were randomised to vPDT and received treatment at Day 1 with verteporfin 6 mg/m² IVT for 10 minutes, followed 15 minutes after the start of the infusion by laser scanning frequency (SF) rate of 600 mW/cm² for 83 seconds with light dose of 50 J/cm². 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 (full analysis set (FAS)/modified last observation carried forward (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 least-squares means (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) it 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% confidence interval (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 visual acuity (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), 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 I, 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 Central Retinal Thickness (CRT) over time, change in Central Foveal Thickness (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.

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 (standard deviation (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.

Exploratory Phase II study (REPAIR)-limited supportive data

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 period of the 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 fundus photography (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.

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 relevant TGA adopted EU Guideline⁴. 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. 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 76 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.

Safety

Studies providing 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.

⁴ CPMP/EWP/2330/99), *Points to Consider on application with 1. Meta-analyses; 2. One pivotal study*

In this clinical evaluation, 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.

Patient exposure

In this study, patients received either ranibizumab at 0.5 mg/0.05 mL and/or vPDT at 6 mg/m² followed by a SF rate of 600 mW/cm² delivered for 83 seconds with light dose of 50 J/cm². 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 adverse events (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 prior to Month 3 and were reported in Group II for all safety analyses but were excluded from the Month 3 and 6 Per protocol (PP) sets. The safety set for the safety analyses at different periods is summarized below in Table 2.

Table 2. CRFB002F2301 – Safety analysis periods; safety set.

Safety analysis periods	Ranibizumab 0.5 mg			vPDT		Total n (%)
	Group I by stabilization	Group II by disease activity	Group III prior to Month 3	Group III with 0.5 mg ranibizumab from Month 3	Group III without 0.5 mg ranibizumab from Month 3	
	n (%)	n (%)	n (%)	n (%)	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.						

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 to 4 injections, and 50.0% (59/118) of patients in Group II received 1 to 2 injections. The numbers of ranibizumab injections received by patients up to Month 6 and up to Month 12 were summarised in the submission.

In Group III (vPDT), of the 53 patients in the safety set 38 (71.7%) patients were treated with ranibizumab from Month 3 through 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.

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 3. 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 3. 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 11 was 45.8% (54/118), 34.7% (41/118), 16.9% (20/118), 17.0% (19/112), and 13.4% (15/112), respectively.

Postmarketing data

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 postmarketing 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).

Evaluator's 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.

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.

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 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 $\geq 2\%$ 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 $\geq 2\%$ 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%), intra ocular pressure (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 $\geq 2\%$ 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).

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 $\geq 2\%$ 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 $\geq 2\%$ 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 $\geq 2\%$ 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%).

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 category (PT uveitis: 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%). 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 category (PT uveitis: 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 category (PT ocular hypertension: 1, 5.3%).

Ocular safety concerns in the study eye from Baseline up to Month 12 in patients in Group I were endophthalmitis category (PT uveitis: 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 category (PT ocular hypertension: 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%), transient IOP increased (4, 10.5%) and glaucoma category (PT ocular hypertension: 1, 2.6%), 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.

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 $\geq 2\%$ 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 45.3% of patients in Group I and 43.2% of patients in Group II. Non-ocular AEs reported in $\geq 2\%$ 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%).

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.

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

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 serious AE (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 hospitalised and received concomitant treatment resulting in the resolution of the event on Day 43. One patient in Group II experienced an ocular SAE of moderate retinoschisis after Month 6 (Day 309) which was 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 Medical Dictionary for Regulatory Activities (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.

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.

First round benefit-risk assessment

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 I 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 $p \leq 0.001$ 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.

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), 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 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).

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 month period 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 was reported more than once.

No SAEs of endophthalmitis were reported in the study. However, endophthalmitis categorised 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 $\geq 1\%$ 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 $\geq 1\%$ 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; 2 visual impairment, 1 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 category (PT uveitis n=1, 0.9%), 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 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.

First round assessment of benefit-risk balance

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.

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).

Clinical questions

Efficacy

1. In 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 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 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.

Safety

4. Were the ocular AEs described in the Phase II ('supportive') study CRFB002AGB10 for the study eye only or for the study eye plus the fellow eye?

Second round evaluation of clinical data submitted in response to questions

The sponsor provided complete responses to the *Clinical Questions* raised following the first round evaluation of the submission. For details of the sponsor's responses and the evaluator's comments on these responses see Attachment 2.

Second round benefit-risk assessment

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.

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.

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.

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).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan Core Safety Risk Management Plan, version 11.1, dated 19 December 2012; Australian Specific Annex (ASA), version 1.0, dated 7 June 2013 and RMP and ASA provided in response to the TGA's request (EU-RMP, version 12.1, dated 14 August 2013 with Australian Specific Annex, version 2.0, dated 20 December 2013) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

Table 4. Summary of ongoing safety concerns

Important identified risks	
	Hypersensitivity reactions RPE tear Endophthalmitis Retinal detachment Retinal tear Cataract Intraocular inflammation Intraocular pressure increase Vitreous hemorrhage
Important potential risks	
	Hypertension Non-ocular hemorrhage Proteinuria Myocardial infarction Non-myocardial Arterial thromboembolic events Venous thromboembolic events Deterioration of retinal blood flow including CRAO Glaucoma
Important missing information	
	Systemic AEs related to bilateral treatment and overdose AEs related to off-label use, including potential local and systemic AEs related to pediatric off-label use (e.g. retinopathy of prematurity [ROP]) Long-term safety two years and beyond Intraocular antibody formation Long term effects on the progression of diabetic retinopathy including the potential effect on diabetic retinopathy of stopping periodic anti-VEGF injections (DME) Effects of ranibizumab on the deterioration of retinal blood flow including macular ischemia (DME) Systemically unstable patients (DME) Age greater than 75 years (DME) Ethnicities other than Caucasian (DME and RVO) Long term effects on the progression of the condition (PM)

Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specifications, it is considered that this table of ongoing safety concerns is not acceptable.

The European Public Assessment Report (EPAR) for the product which refers to EU-RMP version 11.2 contains the missing information of '*Visudyne (verteporfin plus PDT) or laser photocoagulation given in combination with ranibizumab (PM)*'. Routine risk minimisation activities in form of provision of information in the EU-Summary of Product Characteristics (SmPc) are assigned to this missing information, with the details as shown below (table taken from the EPAR for Lucentis, dated 30 May 2013).

Table 5. Safety concern: Visudyne (verteporfin plus PDT) or laser photocoagulation given in combination with ranibizumab (PM) [from EPAR for Lucentis]

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Visudyne (verteporfin plus PDT) or laser photocoagulation given in combination with ranibizumab (PM)	The lack of data on combination of Lucentis with Visudyne or laser treatment of pathologic myopia is described in SmPC Section 4.2: Lucentis and Visudyne photodynamic therapy in CNV secondary to PM: There is no experience of concomitant administration of Lucentis and Visudyne.	None.

Visudyne is on the ARTG and supplied in Australia and it is considered standard of care for CNV. It can be assumed that the combination of these two products will be used in

Australia and therefore it appears reasonable this missing information be included in the RMP. It is recommended this missing information be included in the table of ongoing safety concerns. Pharmacovigilance and risk minimisation activities should be assigned to this missing information as appropriate. It appears that the difference in safety specification may be due to the different versions evaluated by EU (EU-RMP version 11.2) and the version submitted to the TGA (CSRMP version 11.1).

Contents of the pharmacovigilance submission

The sponsor proposed routine pharmacovigilance activities and additional pharmacovigilance in the form of studies which are ongoing at the time of this evaluation.

Routine risk minimisation activities are proposed to address most ongoing safety concerns except for most missing information. Additional risk minimisation activities are carried out in the form of an educational program for health care professionals and patients to minimise the risk of Increases in Intraocular Pressure (IOP). The educational materials have not been included in this submission, and recommendations to submit these to the TGA are made in the paragraph below.

The Core Safety RMP (CSRMP) submitted for this application does not comply with the EU-RMP format which is required for evaluation and stated in the document *Risk Management Plan Questions and Answers document (RMP Q&As), version 1.3, dated October 2012*. The submitted CSRMP is missing EU-RMP section 3 'Evaluation of the need for risk minimisation activities', and Annexes such as Annex 8 'Details of proposed educational programme'. The sponsor states:

Changes from previous RMP version: The list below shows the major modifications/changes for Safety Risk Management Plan (RMP) version 11.1 from RMP version 10. Since this is a Core RMP rather than an EU RMP, for all sections, the use of the European summary of product characteristics (EU SmPC) as a source document was replaced with the Core Data Sheet (CDS). The previous Sections 3 and 6 were deleted in accordance with this new Core RMP template.

It is recommended that the sponsor submits the most current EU-RMP version including any Annexes relevant for the RMP evaluation.

The ASA provided for this submission does not include any Australian specific information about the epidemiology of the target disease. It is recommended that the sponsor provides this information, and any other information required to evaluate the Australian specific context of this submission. The information which should be provided is the ASA is outlined in the RMP *Questions and Answers*.

Reconciliation of issues outlined in the RMP report

Table 6 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.'

Table 6. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Extract of sponsor's response	OPR evaluator's comment
1. It is recommended that the sponsor submits the most current EU-RMP version including any Annexes relevant for the RMP Evaluation.	As per TGA request the sponsor submitted EU-RMP version 12.1 (dated 14 August 2013), which is the most current version submitted to and approved by the EMA 24 October 2013.	This is considered acceptable.
2. It is recommended that the sponsor provides Australian specific information about the epidemiology of the target disease, and any other information required to evaluate the Australian specific context of this submission.	The sponsor provided the requested information. Furthermore, the sponsor stated: <i>This updated information has been included under section 4 'Anticipated Use in Australia' in the updated ASA v2.0 included with this response.</i>	This is considered acceptable.
3. It is recommended that the missing information of 'Visudyne (verteporfin plus PDT) or laser photocoagulation given in combination with Ranibizumab (PM)' be included in the table of ongoing safety concerns. Pharmacovigilance and risk minimization activities should be assigned to this missing information as appropriate.	The sponsor submitted the EU RMP v12.1, which as mentioned above is the most current version submitted to and approved by the EMA. EU RMP v12.1 contains the missing information 'Visudyne (verteporfin-PDT) or laser photocoagulation given in combination with Ranibizumab (PM)' as part of Table 9.1 Summary of safety concerns. Routine pharmacovigilance activities including review in Periodic Safety Update Report (PSURs) and long-term observational study (LUMINOUS) are assigned to this missing information to assess the safety of Visudyne (verteporfin-PDT) or laser photocoagulation given in combination with ranibizumab in the treatment of PM. Currently no risk minimisation measures are proposed for this missing information as no specific safety concerns were observed in clinical trials to date. The Core Data Sheet and Australian PI will be updated should any new concerns develop during on-going safety reviews.	It is noted that the sponsor states: <i>Currently no risk minimisation measures are proposed for this missing information as no specific safety concerns were observed in clinical trials to date. The Core Data Sheet and Australian PI will be updated should any new concerns develop during on-going safety reviews.</i> However, the sponsor proposes to include the following information in the Australian PI in section 'Treatment of visual impairment due to CNV secondary to PM': <i>There is no experience in using Lucentis in combination with Visudyne.</i> This information is also reflected in the ASA, version 2.0. Consequently, it appears that the

Recommendation in RMP evaluation report	Extract of sponsor's response	OPR evaluator's comment
		sponsor's response is not accurate to reflect the proposed risk minimisation activities for this ongoing risk. As this represents only a minor error in the sponsor's response document, no further action is required by the sponsor.
4. The following minor changes to the ASA are recommended: A.) It is recommended that the sponsor amends the ASA to describe follow-up questionnaires/checklists as routine Pharmacovigilance when the next update of the ASA occurs. B.) It is recommended that the sponsor removes the Epi-Cohort and RESTORE study from the table of outstanding milestones.	Novartis has amended the ASA to describe follow-up questionnaires/checklists as routine pharmacovigilance. Please find an updated ASA v2.0 included with this response. The status of studies CRFB002A2401 (Epi-COHORT) and CRFB002D2301E1 (RESTORE extension) have been updated in this ASA to 'Completed'. A brief summary of results of these studies have been included in EU RMP v12.1.	This is considered acceptable.
5. The studies referenced in the Pharmacovigilance plan will generate safety data that will simply support the known safety profile of the medicine, while others will generate data that will provoke applications to amend the Australian registration details. To this end it is recommended that the sponsor provides an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	Submission of study reports to the TGA for ongoing or completed studies of the pharmacovigilance plan is not planned. These are available upon request by the TGA. Novartis has amended Section 5.2 of the ASA to reflect this information. Should any new safety concerns arise from a study, Novartis would submit the relevant CSR(s) to the TGA and update the Lucentis Core Data Sheet and Australian PI accordingly.	This is considered acceptable.
6. The RMP evaluator would like to draw this to the delegate's attention to consider whether a decrease in	The RMP evaluator has noted that similar products used for intravitreal injections, supplied in the same presentation are provided with a volume of 100 µL. The volume referred to by this similar	This is considered acceptable.

Recommendation in RMP evaluation report	Extract of sponsor's response	OPR evaluator's comment
<p>the product volume supplied might be in the interest of patients and their communities in terms of a lowered potential of medication errors and lower product costs.</p>	<p>product (aflibercept), actually refers to the extractable volume. The AusPAR for aflibercept identifies the target fill volume as 278 µL. Therefore, this intravitreal injection has a fill volume of 0.278 mL, which is a larger volume than that contained within the Lucentis vial. As noted in the response provided previously, a filling volume of 0.23 mL was chosen by Novartis to prevent multiple uses whilst enabling the required amount of ranibizumab solution for injection for one dose to be withdrawn. To support this fill volume, a study was undertaken in which different fill volumes were tested by medically qualified subjects. This study was provided during the aforementioned submission. A copy of this study was.</p>	
<p>7. It is recommended that a survey be conducted on a periodic basis to ensure the ongoing effectiveness of the educational materials. The results of these surveys should be submitted to the TGA on a periodic basis.</p>	<p>Lucentis was first approved in Australia in 2007 for wet age-related macular degeneration (wAMD) and in 2011 for both retinal vein occlusion (RVO) and diabetic macular oedema (DME) indications. With these additional extensions of use, Lucentis has continued to be prescribed and administered in the same way by the same specialists. This will also be the case for the proposed indication of pathologic myopia (PM). Novartis conducted a survey to evaluate the effectiveness of the Lucentis healthcare professional educational materials between March and April 2009. The survey revealed a good understanding and knowledge of the educational materials for risks associated with intravitreal injection. The full results of this survey were submitted with PSUR6 (reporting period 1 January 2009 to 30 June 2009) to the TGA and the EMA, and the issue was considered closed by the EMA. As the materials tested in this survey were in relation to the correct IVT technique, it is independent of indication. As stated in EU RMP V12.1, and approved by the EMA with the application to extend the indications for the treatment of PM in the EU, the effectiveness of risk minimization measures is assessed by measuring the reporting rates of endophthalmitis, cataracts, increased intraocular pressure and overdose due to overfill of the prefilled syringe. The reporting rates of endophthalmitis, cataracts, increased intraocular pressure</p>	<p>This is considered acceptable.</p>

Recommendation in RMP evaluation report	Extract of sponsor's response	OPR evaluator's comment
	<p>from spontaneous and literature cases have remained essentially stable over the time period that the educational materials have been in use. The analysis of these risks and new potential risk 'Overdose due to overfill of the pre-filled syringe' is ongoing and will be reported to the TGA via PSURs (Note: Potential risk 'Overdose due to overfill of the pre-filled syringe' was recently added to EU RMP v12.1, and will be included in subsequent PSUR reports). Novartis considers the results of the survey conducted in 2009 still to be valid and no further surveys to evaluate the effectiveness of educational materials are planned at this time.</p>	
<p>8. It is recommended that the sponsor submits these educational materials for review prior to approval. Furthermore, it is recommended that the sponsor provides an outline on how the TGA approved educational materials will be amended if this extension of indication will be approved.</p>	<p>Lucentis educational materials currently in use were provided to TGA 10 July 2013. A copy of EU educational materials that will be adapted for local use in Australia were submitted with this response. These materials include information on the newly proposed indication for pathological myopia.</p>	<p>It is recommended that the educational materials adapted for use in Australia, be provided to the TGA for review, prior to distribution in Australia.</p>
<p>9. It is recommended that the sponsor provides a tabular 'Summary of the Risk Management Plan in Australia' in a revised ASA, pertaining to specific wording by which risk minimization is exercised in the Australian PI/CMI.</p>	<p>An updated ASA v2.0 was included with the sponsor's response. The table outlining safety concerns and where respective information has been included in the Australian Product Information has been updated to include specific wording exercised in the Australian PI.</p>	<p>This is considered acceptable.</p>
<p>10. It is recommended that a statement be added in the <i>Dosage and Administration</i> section informing healthcare professionals that there is no experience in using Lucentis in combination with Visudyne.'</p>	<p>Novartis acknowledge the recommendation made by the RMP evaluator and have amended the PI accordingly.</p>	<p>This is considered acceptable.</p>

Summary of recommendations

It is considered that the sponsor's response to the TGA request has not adequately addressed all of the issues identified in the RMP evaluation report (see *Outstanding issues* below).

Outstanding issues

Issues in relation to the RMP

1. It is recommended that the educational materials adapted for use in Australia, be provided to the TGA for review, prior to distribution in Australia.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Comments on the safety specification of the RMP

First round comments on clinical aspects of the Safety Specification in the draft RMP: The clinical aspects of the Safety Specification in the draft RMP are satisfactory.

Second round comments on clinical aspects of the Safety Specification in the draft RMP: The sponsor's response of 23 December 2013 included the most current RMP submitted to and approved by the EMA: that is, EU Safety Risk Management Plan (RMP) Version 12.1 for pre-filled syringe submission, 'final sign off date' of 14 August 2013. In addition, the sponsor's response included an Australian Specific Annex (ASA) with a 'release date' of 20 December 2013. The clinical aspects of the Safety Specification in the EU RMP (V12.1) relating to 'pathologic myopia (PM)' are satisfactory.

Key changes to the updated RMP

In their response to the TGA, the sponsor provided an updated EU-RMP, version 12.1, dated 14 August 2013 with Australian Specific Annex, version 2.0, dated 20 December 2013. Key changes from the version evaluated at Round 1 are summarised below:

Table 7. Key changes to the RMP

Safety specification	<ol style="list-style-type: none"> 1.) The important potential risk of 'Overdose due to overfill of the pre-filled syringe' has been added to the updated version of the RMP. 2.) The important missing information of 'Visudyne (verteporfin-PDT) or laser photocoagulation given in combination with ranibizumab (PM)' is included in the updated version of the RMP.
Pharmacovigilance activities	<ol style="list-style-type: none"> 1.) Routine pharmacovigilance activities including review in PSURs. 2.) Routine pharmacovigilance activities including review in PSURs. Long-term observational study (LUMINOUS).
Risk minimisation activities	<ol style="list-style-type: none"> 1.) Provision of information in the PI and Health care professional educational materials. 2.) Provision of information in the PI.

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented (see below).

Suggested wording for conditions of registration***RMP***

Implement EU-RMP, version 12.1, dated 14 August 2013 with Australian Specific Annex, version 2.0, dated 20 December 2013 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

The clinical data consisted of one pivotal Phase III, controlled study (RFB002F2301; RADIANCE) and one Phase II, uncontrolled study (CRFB002AGB10; REPAIR). These are briefly described below. Please see the accompanying TGA clinical evaluation report (CER) for details (Attachment 2).

The clinical evaluator recommended approval.

No dose selection study was performed for the new indication. The proposed dose (0.5 mg) was chosen based on the current approvals in related indications.

Verteporfin (Visudyne) photodynamic therapy (vPDT) is currently approved in Australia for the treatment of patients with subfoveal choroidal neovascularisation due to age-related macular degeneration or patients with subfoveal choroidal neovascularisation caused by 'other' macular diseases. This may be considered as applying to myopia indication. A clinical trial of vPDT in PM is described in the approved Visudyne PI. Verteporfin is given IVT over 10 minutes followed by activation of drug by non-thermal red light and is not given more frequently than every 3 months. This was used as the active comparator in the pivotal trial (RADIANCE) to ascertain relative efficacy of intravitreal ranibizumab in this indication.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical**Clinical Efficacy in PM*****Pivotal efficacy study (RADIANCE)***

This was a Phase III, randomised, double-blind, active-controlled study in which two ranibizumab (0.5mg dose) groups (retreatment defined by stabilization criteria OR retreatment defined by disease activity criteria) were compared with vPDT in the treatment of adult (≥ 18 years age) patients with visual impairment due to CNV secondary to PM. This primary comparison with the active comparator (vPDT) was at the Month 3 time point. The 2 ranibizumab groups were mutually compared at Month 6. The total duration of study was 12 months. The relevant masking (vPDT or ranibizumab sham) was maintained for 12 months.

The main inclusion criteria for were active CNV secondary to PM with > -6 D spherical equivalence and anteroposterior elongation ≥ 26 mm; at least one lesion type (subfoveal, juxtafoveal, extrafoveal margin of the optic disc) in the study eye; baseline best corrected visual acuity (BCVA) ≥ 24 letters and ≤ 78 letters tested using Early Treatment Diabetic Retinopathy Study (ETDRS) like VA chart (equivalent to 20/32 to 20/320 on Snellen chart).

The main exclusion criteria included ocular disorders in the study eye that could confound study results, compromised VA or required medical or surgical intervention during the 12 month study period (including retinal detachment, cataract and pre-retinal membrane of the macula); history of pan-retinal or focal/grid laser photocoagulation with involvement of the macular area in the study eye at any time; history of intraocular treatment with any anti-VEGF or vPDT at any time in the study eye; history of intra-ocular surgery or treatment with corticosteroids in preceding 3 months.

The patients were monitored monthly throughout the study and were retreated based on stabilization and/or disease activity criteria.

Stabilization was defined as no change in BCVA compared with the two preceding monthly evaluations.

Disease activity was defined as vision impairment attributable to intra-retinal or subretinal fluid or active leakage due to the CNV secondary to PM as assessed by Optical Coherence Tomography (OCT) and/or Fluorescein Angiography (FA).

If both eyes were considered eligible, the eye with the worse VA was selected for study treatment. However, the investigator could select the eye with better VA, based on medical reasons and according to local ethical requirements. The eligible patients ($N = 277$) were randomised to 3 treatment groups (2:2:1) as follows:

- Group I $n = 106$; retreatment driven by BCVA stabilization; patients received 0.5mg ranibizumab intravitreal injection at Day 1 *and* Month 1. BCVA stabilization was assessed monthly. Further dosing was stopped if the stabilization criteria were fulfilled. Retreatment was resumed with monthly injections where there was loss of VA and was continued until stable VA was reached for 3 consecutive monthly assessments.
- Group II $n = 116$; retreatment driven by disease activity criteria; patients received 0.5 mg ranibizumab intravitreal injection on Day 1. Patients were monitored monthly and retreatment was not given if no disease activity was seen, and retreatment was given when disease activity criteria were observed.
- Group III ($n = 55$); vPDT group; patients received vPDT at Day 1 but no further treatment was given at Months 1 or 2. Patients were monitored monthly. From Month 3 to 12, the investigator could administer 0.5 mg ranibizumab or vPDT or ranibizumab/vPDT combination based on the disease activity criteria. Of the 55 patients in Group III, 38 received ranibizumab alone from Month 3 to Month 12 and 15 patients received vPDT alone from Month 3 to 12. Two patients received ranibizumab prior to Month 3 (protocol deviation). No patient received ranibizumab/vPDT combination.

The mean (SD) age of all randomised patients was 55.5 (13.94) years (range 18 to 87 years) with about 20% patients < 45 years of age. The mean (SD) baseline BCVA was 55.4 (13.11) letters (range 8 to 83). In each of the 3 groups approximately 70% of patients had baseline BCVA > 45 letters. The mean (SD) axial length at baseline was 29.07 (1.892) mm (range 22.2 to 36.1 mm). The mean axial length was similar in the 3 treatment groups (28.75 to 29.37 mm). The mean refraction-sphere at baseline was -12 diopters (range -6 to -30). Overall, the baseline CRT and the distribution of CNV location subtype were

comparable. Overall, patients had subfoveal (68.6%), juxtafoveal (23.8%) and extrafoveal (4.0%) lesions.

The primary efficacy outcome was change in BCVA (letters) from baseline to the average of BCVA over Months 1 to 3. Two primary efficacy analyses were performed at Month 3 time point, that is, Group I (ranibizumab by stabilization) versus Group III (vPDT) and Group II (ranibizumab by disease activity) versus Group III (vPDT). These were intended superiority comparisons.

The main secondary efficacy analysis was at Month 6, that is, pairwise efficacy comparison of the two ranibizumab groups with each other. This was intended non-inferiority comparison. There were a number of additional secondary and exploratory efficacy outcomes. The main results were as follows:

Month 3

At Baseline, mean (SD) BCVA in the study eye was 55.4 (13.43), 55.8 (12.59) and 54.7 (13.84) letters in Groups I, II and III respectively.

At Month 3, the mean (SD) BCVA in the study eye over Months 1 to 3 was 66.0 (12.98), 66.4 (12.28) and 56.9 (14.49) letters in the 3 groups respectively.

Thus, the mean (SD) change in BCVA in the study eye from Baseline to Month 3 was 10.5 (8.16), 10.6 (7.26) and 2.2 (9.47) letters in the 3 groups respectively.

The Treatment Difference in BCVA at Month 3 for ranibizumab (Group I) versus vPDT (Group III) was 8.5 letters (95%CI 5.8, 11.2) in favour of ranibizumab treatment.

The Treatment Difference in BCVA at Month 3 for ranibizumab (Group II) versus vPDT (Group III) was 8.6 letters (95%CI 6.1, 11.1) in favour of ranibizumab treatment.

Month 6

At Month 6, the mean (SD) BCVA in the study eye was 67.3 (12.40) and 67.5 (12.34) letters in Groups I and II respectively.

The mean (SD) change in BCVA in the study eye from Baseline to Month 6 time point was 11.9 (8.81) and 11.7 (8.24) letters in Group I and II respectively.

The Treatment Difference in BCVA at Month 6 for Group II versus Group I comparison was -0.1 (95%CI -2.2, 2.0) letters indicating similar effect (non-inferior) in the two ranibizumab groups.

Month 12

At Month 12, the mean (SD) BCVA in the study eye was 68.3 (12.61) and 68.3 (12.45) letters in Group I and II respectively.

The mean (SD) change in BCVA from Baseline to Month 12 time point was 12.8 (9.48) and 12.5 (8.83) letters in Groups I and II respectively indicating maintenance of effect at Month 12.

In Group III, 40/55 (73%) patients, initially treated with vPDT, received retreatment with ranibizumab from Month 3 to Month 12. At Month 12, mean (SD) BCVA in the study eye was 61.1 (14.86) letters in this group indicating a mean (SD) change of 6.4 (9.55) letters.

The proportion of patients who gained ≥ 15 letters (or reached BCVA ≥ 84 letters) from Baseline was 38.1%, 43.1% and 14.5% (Month 3), 46.7%, 44.8% and 27.3% (Month 6) and 53.3%, 51.7% and 32.7% (Month 12) patients in Groups I, II and III respectively.

The proportion of patients who gained ≥ 10 letters (or reached a BCVA of ≥ 84 letters) was 61.9%, 65.5%, and 27.3% (Month 3), 71.4%, 64.7%, and 45.5% (Month 6) and 69.5%, 69.0%, and 49.1% (Month 12) in Groups I, II, and III respectively.

The proportion of patients who lost ≥ 15 letters BCVA from Baseline was 1.9%, 0% and 7.3% (Month 3), 0%, 0.9%, and 3.6% (Month 6) and 1.9%, 0.9%, and 3.6% (Month 12) in Groups I, II and III respectively.

The proportion of patients who lost ≥ 10 letters BCVA was 1.9%, 0.9%, and 16.4% (Month 3), 1.9%, 2.6%, and 3.6% (Month 6) and 4.8%, 1.7%, and 3.6% (Month 12) in Groups I, II and III respectively.

For retinal/anatomical/lesion changes as well as patient reported outcomes, please see the accompanying CER.

Retreatment

As noted above, the Group I patients received 2 injections of ranibizumab on Day 1 and Month 1. The Group II patients received one ranibizumab injection on Day 1. Monthly monitoring was performed in all groups.

The mean \pm SD number of ranibizumab injections received up to Month 3 (primary time point) was 2.5 ± 0.57 (range 1-3) in Group 1 and 1.8 ± 0.82 (range 1-3) in Group II. This lower average use in Group I compared to Group II was maintained at Month 6 (3.5 ± 1.46 (range 1-6) in Group 1 versus 2.5 ± 1.56 (range 1-6) in Group II) and at Month 12 (4.6 ± 2.59 (range: 1-11) in Group I versus 3.5 ± 2.92 (range 1-12) in Group II).

The percentage of patients who achieved interruption after the minimal number of injections, that is, protocol specified 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 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, single injection).

In Group I, 20.4% (21/103) patients had the maximum duration of treatment free interval possible for this group, that is, 10 months. In Group II, 28.8% (32/111) patients had the maximum duration of treatment free interval possible for this group, that is, 11 months.

Re-initiation of treatment, that is, treatment administered after a visit without treatment, occurred in 55.3% (57/103) patients with interrupted treatment in Group I and 46.9% (52/111) patients with interrupted treatment in Group II. The mean number of consecutive injections during the first re-initiation of treatment was 2.1 in Group 1 and 1.5 in Groups II.

In Group III, the mean number of ranibizumab injections from Month 3 was 1.9 up to Month 6 and 3.2 up to Month 12. A total of 15 Group III patients did not receive any ranibizumab injection (that is, received repeat vPDT treatment). No patient received combined ranibizumab/vPDT.

Supportive efficacy study (REPAIR)

This was a 12 months study of uncontrolled treatment with ranibizumab in adult patients with CNV secondary to PM. All patients were treated with an initial dose of intravitreal ranibizumab 0.5 mg, followed by repeated monthly administration, as needed, for up to a further 11 months. However, vPDT was allowed as rescue therapy at the investigator's discretion. The inclusion/exclusion criteria were similar to the pivotal study above.

A total of 65 patients took part in the study. The mean (SD) age was 55.5 (14.97) years (range 21 to 92 years). The mean (SD) duration of CNV was 1.78 (3.26) months. The mean (SD) duration of PM was 39.89 (20.52) years. The mean (SD) baseline BCVA in the study eye was 59.5 (13.58) letters (range 26 to 85 letters). 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 was 1.463 (1.3511) mm² (range 0.12 to 6.56 mm²). The results were as follows:

At Baseline, the mean (SD) BCVA was 59.5 (13.58) (range 26 to 85 letters). At Month 12 the BCA improved to a mean (SD) of 73.1 (13.13) letters (range 27 to 94). A total of 24 (36.9%) patients gained a BCVA of ≥ 15 letters in the study eye, and 33 (50.8%) patients gained of ≥ 10 letters in the study eye compared to 5 (7.7%) patients with gain of BCVA ≥ 15 letters in the fellow eye and 7 (10.8%) patients with a gain of ≥ 10 letters in the fellow eye.

The median number of ranibizumab injections during the 12 months treatment period was 3 (mean 3.6). At least one retreatment was required in 51 patients (78.5%). The most frequent number of retreatments were one (18.5%), two (16.9%) and three (15.4%). Two patients received the maximum possible 12 injections. The median time to first retreatment was 2 months (95%CI 1.25, 3.42). The Kaplan-Meier plot indicated that patients requiring retreatment did so within 8 months of the baseline injection.

Clinical safety

The pivotal efficacy study (RADIANCE) included 262/277 ranibizumab treated patients including 106 in Group I, 118 in Group II, 38 in Group III (vPDT patients who received any ranibizumab after Month 3) and another 15 in Group III (vPDT patients who did not receive any ranibizumab after Month 3) over 12 months. Two patients in Group III received ranibizumab prior to Month 3 and are included in Group II for safety analysis. The uncontrolled supportive efficacy study (REPAIR) consisted of 65 patients who all received IVT ranibizumab over 12 months.

For details of the reported adverse events (AEs) in these please see Attachment 2.

Overall, adverse effects profile of intravitreal 0.5mg ranibizumab for the proposed use in PM was consistent with the known profile of ranibizumab in the currently approved indications.

Ocular safety concerns in relation to intravitreal ranibizumab identified in the RMP include endophthalmitis, intraocular inflammation, cataract, transient IOP increased, deterioration of retinal blood flow, retinal tear, retinal detachment, retinal pigment epithelial tear, vitreous haemorrhage and glaucoma. Ocular safety concerns identified in the fellow eye include cataract, transient IOP increased, deterioration of retinal blood flow, intraocular inflammation and glaucoma.

Systemic safety concerns identified in relation to intravitreal ranibizumab use include hypersensitivity, hypertension, non-ocular haemorrhage, proteinuria, myocardial infarction, other arterial thromboembolic events and venous thromboembolic events.

No case of 'retinal detachment' was reported in the two studies included in this submission. Three events (1.3%) coded as 'retinal tear' were reported for 2 patients in Group I and 1 patient in Group II in the pivotal efficacy study. This incidence (1.3%) is stated to be higher than that seen in other indications (0 to 1.1% in wet AMD, 0 to 0.8% in DME and in RVO). The sponsor argues that this likely represents risk from the underlying pathology (PM) rather than the treatment.

At present, there are no data for treatment beyond 12 months. The data in patients with extrafoveal CNV are limited to 11/277 patients in the pivotal study. Data on bilateral use and data in children/adolescents are also lacking.

Clinical evaluator's recommendation

The clinical evaluator concluded that 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.

Risk management plan

Advice from ACSOM was not sought for this submission. The OPR evaluator recommends implementation of EU-RMP, version 12.1, dated 14 August 2013 with Australian Specific Annex, version 2.0, dated 20 December 2013 and any future updates as a condition of registration.

Risk-benefit analysis

Delegate's conclusion and request for ACPM advice

This is an application for extension of indication for intravitreal ranibizumab 0.5 mg to the treatment of visual impairment caused by choroidal (subfoveal; juxtafoveal; extrafoveal) neovascularisation (CNV) secondary to pathologic myopia (PM).

The dose selected for use in PM (0.5 mg ranibizumab) was arbitrarily based on the currently approved dose in approved conditions. This is considered acceptable.

A randomised, active-controlled trial demonstrated a statistically significant improvement in BCVA of about 8.5 letters at 3 months compared to treatment with vPDT. Although this magnitude of improvement in functional vision is considered clinically meaningful, the mean BCVA with ranibizumab treatment at 3 months was 66 letters compared to the baseline 55 letters, that is, it was still below the upper limit of inclusion criteria (78 letters) for eligibility to participate in this trial. However, the discrete responder analysis showed that nearly 40% patients achieved at least 15 letters improvement (or at least 84 letters BCVA) and nearly 60% patients achieved at least 10 letters improvement at 3 months.

Monthly monitoring was undertaken in all groups but the two ranibizumab treatment groups (0.5 mg dose in both) differed with respect to retreatment criteria (stabilisation OR disease activity). The observed treatment difference between the two ranibizumab groups at this time point was negligible (change in BCVA 11.9 letters versus 11.7 letters in Groups I and II respectively). The non-inferiority was formally demonstrated (95%CI for the treatment difference -2.2 to 2.0 letters) based on the pre specified non-inferiority margin of 5 letters.

The 12 months mean BCVA data indicated maintenance of effect (BCVA) at 12 months in both ranibizumab groups at levels similar to those at 6 months. There was steady increase in the percentage of responders (gain of ≥ 15 letters or ≥ 10 letters) at 6 and 12 months.

The 12 months data in Group III (vPDT) indicated similar benefit with the introduction of ranibizumab treatment after 3 months. The sponsor is requested to provide descriptive data (mean BCVA; responder analyses) in the 15 Group III patients who received vPDT alone during the whole of 12 months compared with the patients in Groups I and II at months 3, 6 and 12 in their pre Advisory Committee on Prescription Medicines.

The risks (ocular/systemic) with intravitreal ranibizumab are well known and the data in the current dossier conforms to that profile. A slightly higher rate of retinal tear was reported in the pivotal efficacy study in PM.

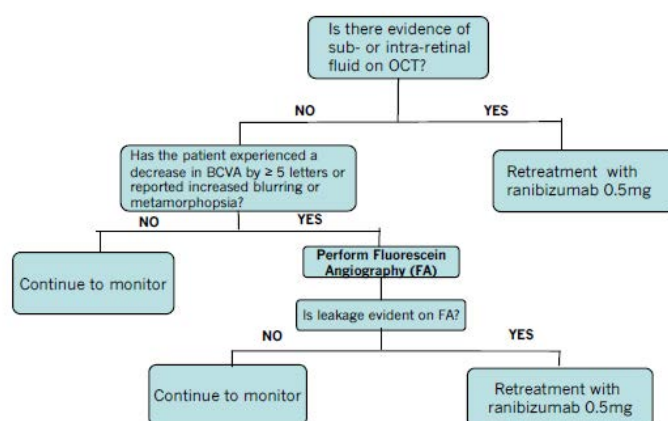
The sponsor is proposing monitoring criteria based on disease activity (Group II) and monthly monitoring frequency only for the first two months, followed by (at least) once every 3 months. After first year, the monitoring frequency is to be determined by the treating physician.

This proposal is consistent with that approved in Europe but is not based on the regime used in the PM clinical trial. This issue was raised with the sponsor during the first round evaluation. The sponsor provided detailed argument in support of the proposed monitoring including statistical modelling which indicated that monthly review for 2 months followed by once every 3 months will capture most instances requiring retreatment using disease activity criteria.

The Delegate considers the argument acceptable and support the proposal. The proposed regimen does not explicitly state but does imply recommencing monthly reviews once retreatment is needed after interruption. This may need to be clarified. The sponsor is requested to provide comment.

The treatment effect could not be ascertained from the uncontrolled data (some useful comparison with the follow eye was provided) but the occurrence of effect was similar to that seen in the pivotal study. The study, however, appears to have used the following algorithm for assessing retreatment (Figure 1):

Figure 1. REPAIR study Retreatment criteria



The sponsor is requested to indicate whether similar decision tree was used in the pivotal efficacy study and whether it will be valid to use it for providing more information to the physicians by its inclusion in the PI.

Overall, the Delegate considers the submitted the premarket data to be adequate to support the proposed indication (broad application to all lesion location types). A postmarket RMP with Australian specific annex agreed with the TGA applies to this submission.

The supported therapeutic indication is as follows:

Treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathological myopia (PM)

The proposed monitoring regime is as follows and is also supported based on argument:

The recommended dose of Lucentis is 0.5mg (0.05 mL) given as a single intravitreal injection.

Treatment is initiated with a single injection.

If monitoring reveals signs of disease activity e.g. reduced visual acuity and/or signs of lesion activity, further treatment is recommended. While many patients may only need one or two injections during the first year, some patients may need more frequent treatment.

Therefore, monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician (see Clinical Trials).

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

There is no experience in using Lucentis in combination with Visudyne.

Delegate's proposed action

The Delegate had no reason to say, at this time, that this application for extension of indication for Lucentis for the treatment of visual impairment in choroidal neovascularisation secondary to pathologic myopia should not be approved.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Validity and appropriateness of the proposed monitoring frequency which is not based on that used in the accompanying pivotal efficacy trial.
2. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Lucentis solution for intravitreal injection containing 2.3 mg/0.23 mL in glass vial and 1.65 mg/0.165 mL in prefilled glass syringe of ranibizumab to have an overall positive benefit-risk profile for the indication;

Treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM) in adults.

In making this recommendation the ACPM

- noted the clinically meaningful improvement in best corrected visual acuity (BCVA) and improved quality of life, while the safety profile was similar to that of Lucentis use in currently approved indications and is well defined.
- Noted that the vial was for single use only but expressed concern at the potential for use as a multi dose vial.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- A *Contraindication* on use in pregnant or lactating women should be appropriately reflected in the relevant sections of the CMI.

- Amendment of the CMI to better reflect Australian circumstances and with reference to the standard CMI template and the Usability Guidelines.

Specific advice

The ACPM advised the following in response to the specific Delegate's questions on this submission:

1. *Validity and appropriateness of the proposed monitoring frequency which is not based on that used in the accompanying pivotal efficacy trial.*

The ACPM advised that the proposed monitoring regime appears acceptable (recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician (see *Clinical Trials*)).

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lucentis (ranibizumab rbe) 2.3 µg/0.23 mL solution for injection vial (AUST R 148325) and 1.65 µg/0.165 mL solution for injection prefilled syringe (AUST R 212387), indicated for:

Lucentis (ranibizumab) is indicated in adults for the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).⁵

Specific conditions of registration applying to these goods

Lucentis (ranibizumab) EU Risk Management Plan (RMP), version 12.1 dated 14 August 2013 with Australian Specific Annex, version 2.0 dated 20 December 2013, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for main Lucentis at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

⁵ **Full indications are now:** *Lucentis ranibizumabj is indicated in adults for:*

- *the treatment of neovascular (wet) age-related macular degeneration (AMD).*
- *the treatment of visual impairment due to diabetic macular oedema (DME).*
- *the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).*
- *the treatment of visual impairment due to choroidal neovascularisation CNV) secondary to pathologic myopia (PM)*

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

<http://www.tga.gov.au>