Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Ranibizumab

Proprietary Product Name: Lucentis

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

December 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications, Changes to Product Information
Decision:	Approved
Date of Decision:	25 October 2011
Active ingredient(s):	Ranibizumab
Product Name(s):	Lucentis
Sponsor's Name and Address:	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
Dose form(s):	Injection solution for intraocular injection
Strength(s):	1.8 mg/0.3 mL and 2.3 mg/0.23 mL
Container(s):	Glass vial (colourless type I glass) with chlorobutyl rubber stopper.
Pack size(s):	One pack contains one vial, one filter needle for withdrawal of the vial contents, one needle for intravitreal injection and one syringe for withdrawal of the vial contents and for intravitreal injection.
Approved Therapeutic use:	Lucentis is indicated 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).
Route(s) of administration:	Intraocular (intravitreal)
Dosage:	0.5 mg each month until visual acuity is stable for 3 consecutive months.
ARTG Number (s):	125968, 148325 (awaiting ARTG change)

Product Background

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, thereby preventing binding of VEGF-A to its receptors.

Binding of VEGF-A to its receptors leads to endothelial cell proliferation and revascularization, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age related macular degeneration, diabetic macular oedema and retinal vein occlusion causing visual impairment.

VEGF also plays a part in embryonic and postnatal vasculogenesis and angiogenesis, skeletal muscle regeneration, cardiac remodelling, endochondrial bone formation, the female reproductive cycle and kidney function.

Ranibizumab (Lucentis) is registered for use in exudative ('wet') macular degeneration; this accounts for 10-15% of cases of macular degeneration. Ranibizumab is the established but not the sole registered treatment for that particular indication. There is an additional anti-VEGF agent (pegaptanib) being marketed for neovascular wet age related macular degeneration (AMD). Ranibizumab was also recently registered for the treatment of visual impairment due to diabetic macular oedema.[1] The current indications for Lucentis are:

Lucentis is indicated for:

- *the treatment of neovascular (wet) age-related macular degeneration (AMD)*
- *the treatment of visual impairment due to diabetic macular oedema (DME)*

This AusPAR describes the evaluation of a submission by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to extend the indications to include:

the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)

The sponsor also proposed to revise the Product Information (PI). The proposed revisions to the PI relate to the *Pharmacokinetics*, *Clinical Trials*, *Indications, Adverse Reactions* and *Dosage and Administration* sections.

RVO is the second leading cause of blindness due to retinal vascular disease after diabetic retinopathy. It is estimated that RVO has a prevalence of 1% to 2% in persons older than 40 years of age, and affects 16 million persons worldwide [Wong and Scott, 2010].[2] In an Australian population prevalence study, the age related increase in RVO prevalence was highly significant ($p<0.001$), and the prevalence for age specific cohorts was 0.7% for subjects < 60 years, 1.2% for subjects 60 to 69 years, 2.1% for subjects 70 to 79 years, and 4.6% for subjects 80 years of age or older [Mitchell et al., 1996].[3] In this study, the prevalence of RVO was 1.6% for both males and females, and there was no significant sex difference after adjusting for age. In an Australian population aged 49 years and older, the 10 year incidence of RVO was 1.6%, and older age (≥ 70 years), increasing mean arterial blood pressure and atherosclerotic retinal vessels were significant predictors of incident RVO [Cugati et al., 2006].[4]

There are two distinct types of RVO classified according to the site of occlusion, branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), and both conditions lead to permeability disorders of the retina caused by the venous occlusion. BRVO involves a more localized area of retina and is characterised by scattered superficial and deep retinal haemorrhages, venous dilatation, intraretinal microvascular abnormalities, and occluded and sheathed retinal venules. In contrast, CRVO involves the entire retina, with scattered superficial and deep retinal haemorrhages and venous dilation. BRVO has been reported with a prevalence of about 3 times that of CRVO [Mitchell et al., 1996].[3] The most common presenting symptom of RVO is an abrupt, painless decrease in central visual acuity (VA) which varies in severity in BRVO and CRVO. Less frequently, patients may present with a history of transient vision loss, lasting a few seconds to minutes, with complete recovery of vision. These symptoms may recur over

[1] TGA, AusPAR for Ranibizumab, November 2011; available at http://www.tga.gov.au/pdf/auspar/auspar-lucentis.pdf.

[2] Wong TY, Scott IU. Retinal-vein occlusion. N Engl J Med 2010; 363:2135-44.

[3] Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia: the Blue Mountains Eye Study. Arch Ophthalmol 1996; 114: 1243-1247.

[4] Cugati S et al. Ten-year incidence if retinal vein occlusion in an older population: the Blue Mountains Eye Study. Arch Ophthalmol 2006; 124: 726-732.

several days to weeks, followed by a decrease in vision that can last more than one year in some patients.

Studies of the natural history of BRVO show that outcome without treatment is variable. A published systematic review of the literature showed that vision was moderately poor (20/40) in eyes with untreated BRVO but generally improved over time with between one third and three quarters of eyes with BRVO showing at least a 2 line improvement in VA, and mean VA improving by 1 letter at 3 months to 15 letters over 18 months with one third to three quarters of patients gaining 2 or more lines of vision without intervention. [Rogers et al., 2010].[5] However, clinically significant improvement beyond 20/40 was uncommon. Over a one year period, between 5% and 15% of BRVO eyes developed macular oedema although of those with macular oedema already present at baseline, 18% to 41% resolved without treatment. The strongest risk factor for BRVO is hypertension but associations have been reported with diabetes mellitus, dyslipidaemias, cigarette smoking and renal disease [Wong and Scott, 2010].[2]

Published studies of the natural history of CRVO show that the outcome of this condition is poor. A published systematic review of the literature showed that for all CRVO cases, including non-ischaemic CRVO, baseline VA was generally poor (20/40) and the majority of studies reported a mean decrease in VA over time [McIntosh et al., 2010].[6] In addition to the risk factors associated with BRVO, glaucoma or elevated intraocular pressure has been associated with CRVO. However, in some patients poor vision persisted despite treatment for raised intraocular pressure.

Laser photocoagulation has been used for more than 20 years for the treatment of BRVO [BVOSG, 1984].[7] This treatment can provide vision stabilisation over the long term and may enable some patients to read an additional 2 lines at 3 years compared with no treatment [Wong and Scott, 2010].[2] However, laser photocoagulation is generally not recommended for the treatment of macular oedema associated with CRVO, although scatter laser photocoagulation has been recommended for the treatment of patients with anterior segment neovascularization [Wong and Scott, 2010]. The only medical (not surgical) treatments approved for both types of RVO are Lucentis in the US (and more recently in the European Union [EU], Canada and Switzerland – see following section) and Ozurdex, a sustained release intravitreal (IVT) implant containing dexamethasone, in the US and EU.

The rationale for the development of ranibizumab as a treatment for RVO is based on the central role VEGF is considered to have in this disease. The normal human retina contains little VEGF, but increased VEGF immunoreactivity has been observed in the vitreous of patients with BRVO and CRVO. The hypoxic environment created in the retina following venous occlusion stimulates the production of VEGF, which ultimately leads to increased retinal capillary permeability and macular oedema. As a result of macular oedema, many patients with RVO experience a loss of visual acuity. Ranibizumab acts by diffusing from the vitreous through the retina to the choroid to bind to active VEGF isoforms and cleavage products. Consequently, the drug inhibits the action of VEGF resulting in reduction of vascular permeability and macular oedema following RVO leading to improved visual acuity.

[5] Rogers SL, McIntosh RL, Lim L et al. Natural history of branch retinal vein occlusion: an evidence-based systemic review. Ophthalmology 2010; 117: 1094-1101.

[6] McIntosh RL, Rogers SL, Lim L, et al. Natural history of central retinal vein occlusion: an evidence-based systemic review. Ophthalmology 2010; 117: 1113-23.

[7] Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol 1984; 98: 271-82.

Regulatory Status

The product received initial ARTG Registration on 19 February 2007.

Lucentis was approved in the USA (22 June 2010) for treatment of patients with:

· *Macular Edema Following Retinal Vein Occlusion (RVO)*

Lucentis was also approved in the European Union (EU) on 27 May 2011 with the indication

Lucentis is indicated in adults for:

· *the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).*

Lucentis was approved in Switzerland on 10 May 2011 with indications identical to those in the EU.

Lucentis was approved in Canada on 25 July 2011 with the indications:

Lucentis (ranibizumab injection) is indicated for:

· *the treatment of visual impairment due to macular edema secondary to retinal vein occlusion (RVO).*

An application is pending in New Zealand.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

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

III. Nonclinical Findings

Nonclinical Summary and Conclusions

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

IV. Clinical Findings

Introduction

The submission included two pivotal clinical efficacy and safety studies supporting the extension of indication to include the treatment of visual impairment due to macular oedema secondary to RVO [CRUISE and BRAVO]. CRUISE included patients with macular oedema secondary to CRVO and BRAVO included patients with macular oedema secondary to BRVO. In addition, the submission also included a population pharmacokinetic report of ranibizumab in patients with RVO [09-3013].

There was currently one additional clinical study of ranibizumab in which the final visit for the last patient was completed on 27 July 2010 [HORIZON, FVF3426g]. This is an uncontrolled, Phase III, open label extension study which includes a cohort of patients (Cohort 2) with RVO who have completed BRAVO [study FVF4165g] or CRUISE [study FVF4166g]. The Clinical Study Report (CSR) from this ongoing Genentech sponsored study

was not provided in the current submission. The sponsor also provided a synopsis of an observational study planned to observe the effectiveness and safety of Lucentis "through individualized patient treatment and associated outcomes".

Pharmacokinetics

Population pharmacokinetics in patients with RVO [09-3013]

Objectives

The objectives of this population pharmacokinetic (PK) analysis were to assess: (a) whether ranibizumab systemic exposure is similar in patients with RVO to that in patients with AMD; and (b) to evaluate the need for dose adjustment based on RVO patient characteristics, specifically effects of covariates on systemic and vitreous pharmacokinetics. Modelling from the previously submitted population pharmacokinetic study in AMD patients was used to assess selected covariate effects on the systemic PKs of ranibizumab in patients with RVO [Study 05-1181]. The investigated covariates included RVO type, renal function, and baseline disease characteristics.

Methods

The population PK analysis included data from the two, pivotal, Phase III studies [BRAVO and CRUISE] in patients with RVO in which ranibizumab was administered as an intravitreal (IVT) bolus injection (0.3 or 0.5 mg) to one eye each month for 6 months, followed by monthly injections on an "as needed" basis for a further 6 months. The basic features of the two studies included in the population PK analysis are summarised below in Table 1.

Table 1: Pivotal Phase III RVO studies included in the analysis

Study (RVO Type)	Ranibizumab Dose (mg/eye)	Dosing Frequency	Concomitant Therapy	Sampling Scheme	No. of Subjects with Measurable Sample/Total (%)	No. of Measurable Samples/ Total (%)
FVF4165g (BRVO)	0.3 and 0.5	Monthly	Laser for some subjects	Day 7 after first dose; day 3, 7, and 14 after third dose; Month 3 and 6 pre-injection	225/261 (86%)	424/871 (49%)
FVF4166g (CRVO)	0.3 and 0.5	Monthly	Laser for some subjects	Day 7 after first dose; day 3, 7, and 14 after third dose; Month 3 and 6 pre-injection	216/259 (83%)	419/870 (48%)

The population PK data were analysed using a conventional non-linear mixed effect model (NONMEM). The methodology, results and predictive performance of the final model were comprehensively described in the study report. Serum concentrations observed from three clinical studies in AMD patients were used for the comparison between patients with RVO and patients with AMD [FVF2128g, FVF2428g and FVF2598g]. Data from these studies were included in the previously submitted and evaluated population PK analysis in AMD patients [Study 05-1181]. The dosing regimen and sampling scheme for these three AMD studies were similar to the pivotal studies in RVO (Table 2).

Table 2: AMD studies included for comparison with RVO studies

Study	Ranibizumab Dose (mg/eye)	Dosing Regimen	Sampling Scheme	No. of Subjects with Measurable Sample/Total (%)	No. of Measurable Samples/Total (%)
FVF2128g	0.3 and 0.5	Monthly	Multiple peaks and troughs, plus Day 14, 42 and 98 samples from all subjects	57/62 (82%)	204/911 (22%)
FVF2428g	0.5	Monthly	Day 7 and 14 samples after the first injection and multiple troughs for all subjects	98/105 (93%)	182/875 (21%)
FVF2598g	0.3 and 0.5	Monthly	Trough concentrations at Months 6, 12 and 24	30/451 (7%)	30/715 (4%)

Database

The final dataset in RVO subjects used for the primary analysis contained a total of 1706 records including 808 measurable concentration–time records and 898 less than reportable (LTR) records from 520 subjects (Table 3).

Table 3: Evaluable serum samples

	Study FVF4165g	Study FVF4166g	All Subjects
No. of subjects treated with ranibizumab	264	261	525
No. of subjects with PK samples collected	261	259	520
No. of subjects with at lease one measurable concentration	225	216	441
No. of total PK samples collected	871	870	1741
No. of measurable PK concentrations	424	419	843
No. of doses/subject			
Mean	5.73	5.7	5.71
Median	6	6	6
Evaluable samples/subject			
Mean	1.88	1.94	1.91
Median	1	1	1
% of evaluable samples per sampling timepoint [a]			
Day 7	96.2%	94.6%	95.4%
Month 2, Day 3	100%	97.5%	98.7%
Month 2, Day 7	96.2%	91%	93.6%
Month 2, Day 14	90.5%	93.5%	92%
Month 2, Day 21	75%	100%	83.3%
Month 3, pre-injection	38.5%	26.2%	32.1%
Month 6, pre-injection	28.1%	27.4%	27.7%

[a] A time range was assigned to each scheduled sampling time point to account for variability in actual sampling time.

To evaluate the need for dose adjustment based on patient characteristics a covariate analysis was conducted using selected covariates. These covariates were chosen because they were found to have some effects on the PK parameters estimated for AMD patients. In addition, several covariates relating to baseline disease status were tested for effects on vitreous elimination of ranibizumab (Ka). Baseline covariates tested in the RVO final population PK analysis using the combined data set from the two pivotal studies are summarised below in Table 4.

Table 4: Covariates in the final RVO population

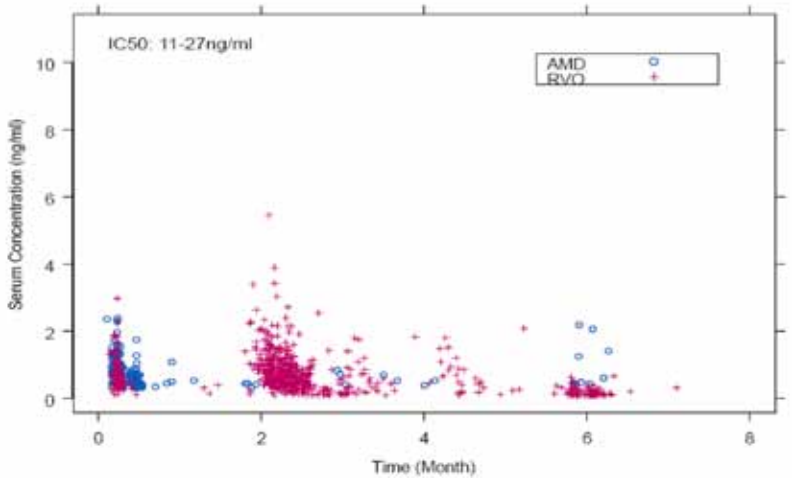
	Age (yr)	CrCL (mL/min)	BLVA (Letter No.)	BCFT (mm)	AONP (mm^2)	TTDX (day)	BIOP (mmHg)	IOP (mmHg)	DIOP (mmHg)
Mean	67.0	87.2	51.4	603	0.638	102	15.0	17.3	2.89
SD	12.2	36.8	13.9	241	1.62	104	3.23	4.52	4.13
Median	67.0	81.1	53.0	587	0	60	15	17	3
5^{th} percentile	46.0	39.3	26.0	236	0	15.0	10	11	–3
95^{th} percentile	84	154	71	1038	4.32	330	20	24	9
Percentage imputed	0	4.84	0	0.255	11.2	0	0	0.382	0.382
Imputed value	NA	81.1	NA	587	0	NA	NA	17	3

ANOP = area of non-perfusion; BCFT = baseline central foveal thickness; BIOP = intraocular pressure before injection; BLVA = baseline visual acuity; CrCL = creatinine clearance; DIOP = difference between BIOP and IOP; IOP = intraocular pressure after injection); NA = not applicable; TTDX = time to diagnosis.

Ranibizumab serum concentrations

The 814 measurable ranibizumab serum concentrations from the two RVO studies at the two dose levels (0.3 and 0.5 mg) were plotted against actual observation times. Overlaid with this plot were 383 ranibizumab serum concentrations from the three AMD studies with the same monthly dose of 0.3 mg or 0.5 mg. The sampling schedules were similar for RVO and AMD studies, except that the RVO studies included additional samples collected after the Month 2 dose (after the third dose). Overall, systemic ranibizumab concentrations following monthly IVT injections of 0.3 or 0.5 mg were reasonably similar for the RVO and AMD populations (Figure 1). At Day 7 after the first dose, where most measurable AMD samples and RVO samples overlapped, the majority of serum concentrations ranged between 0.075 and 2 ng/mL. In both AMD and RVO populations the serum concentrations following monthly 0.3 mg or 0.5 mg IVT dosing were low relative to the concentration necessary to inhibit the biological activity of VEGF-A by 50% (IC_{50} = 11–27 ng/mL).

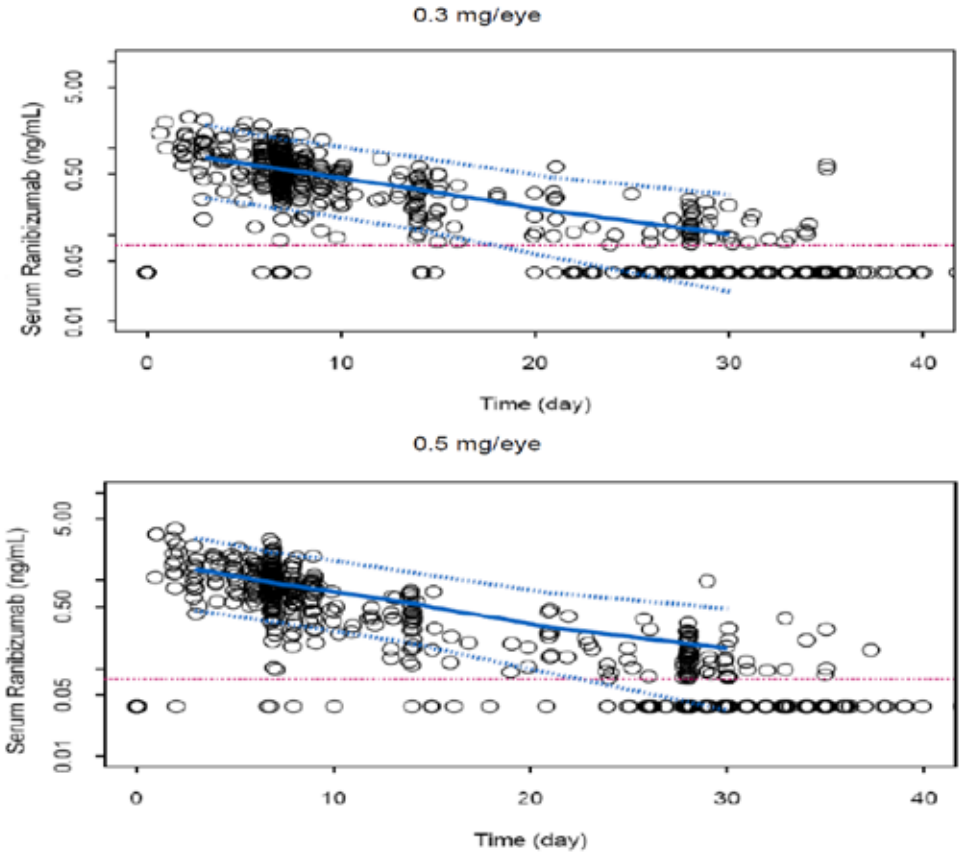
Figure 1: Observed ranibizumab serum concentrations in RVO and AMD patients



Note: Open circles = AMD; Crosses = RVO.

The analysis also included a simulation study which showed that the population PK model derived from the AMD data was able to reasonably well predict the observed concentration data from RVO patients administered IVT ranibizumab. The 90% predicted confidence interval contained the majority of the observed ranibizumab serum concentrations in RVO patients (Figure 2).

Figure 2: Simulated and observed ranibizumab serum concentration in RVO patients using PopPK model in AMD patients following the 0.3 mg dose (upper figure) and the 0.5 mg dose (lower figure)



Note: Time is time elapsed time since last dose. Observed data are plotted in open circles, and median and 5% and 95% of simulated concentrations are showed in solid line and two dash lines, respectively. The lowest level of quantification (LLOQ) (0.075 ng/mL) is represented by the horizontal dotted lines.

Effect of covariates

Population PK estimates for RVO compared with AMD are summarised in Table 5.

Table 5: Population PK estimates, RVO and AMD

Parameter	Parameter estimate (%CV)	
	RVO data	AMD data
Number of patients	441	228
Number of concentrations	843	675
Typical CL/F (L/day)	28.5 (2.11)	23.8 (3.87)
Typical Vc/F (L)	2.54 (fixed)	2.97 (12.4)
Typical Ka (day^{-1})	0.106 (4.53)	0.080 (6.70)
Exponent for CrCL on CL/F	0.627 (10.4)	0.266 (32.2)
Multiplier for PDT on Ka	Not applicable	-0.356 (20.2)
ωCL/F (%)	29.2 (14.6)	31.4 (17.2)
ωVc (%)	80.3 (fixed)	79.3 (25.6)
ωKa (%)	39.4 (33)	30.5 (40.8)
σpop (%)	25.4 (8.82)	36.5 (9.10)
ωCL/F-Ka (%)	17.5 (56.7)	Not applicable

CL/F = apparent systemic clearance; *Vc/F* = apparent central distribution volume; *Ka* = transfer rate constant of drug from vitreous to systemic circulation; *PDT* = photodynamic therapy; ω = standard error of inter-subject variability for random effect distribution; σ = standard deviation describing the proportional component of residual variability; *CV* = coefficient of variation.

None of the covariates tested demonstrated statistically significant or clinically meaningful effects on vitreous elimination (no effects on Ka). This outcome was stated to be similar to that seen previously in AMD patients. In the final model, creatine clearance (CrCL) was the only covariate which had a significant effect on apparent total serum clearance (CL/*F*). This was stated to be similar to the finding in AMD, although the effect was estimated to be numerically greater in patients with RVO than in patients with AMD. In patients with RVO and normal renal function (CrCL > 8 mL/min, 51.8% [n=272]), the mean±standard deviation (SD) ranibizumab CL/F was estimated to be 31.6±10.8 L/day, and the corresponding values for patients with mild impairment (CrCL 50-80 mL/min, 36.4% [n=191]), moderate impairment (CrCL 30-50 mL/min, 9.5% [n=50]) and severe impairment (CrCL < 30 mL/min, 2.3% [n=12]) were 20.5±5.20, 15.9±3.45 and 9.36±3.69 L/day, respectively. These results suggest that systemic exposure to ranibizumab following monthly IVT injection regimens increases in patients with renal impairment defined by baseline CrCL.

However, the anticipated clinical impact of baseline CrCL in RVO patients was assessed by the sponsor to be minimal. Serum ranibizumab concentrations are not believed to contribute to the efficacy of the drug as it is injected by the IVT route and has direct, local effects on retinal vessels. The potential effect on safety of increased ranibizumab systemic exposure in patients with impaired renal function was addressed by comparing observed and simulated systemic exposure relative to the *in vitro* concentration thought to be necessary to inhibit the biological activity of VEGF-A by 50% (that is, 11-27 ng/mL). At all observed and simulated time points ranibizumab concentrations ranged between 0.075 and 2 ng/mL, which was well below the IC_{50}. Therefore, increased systemic exposure associated with impaired renal function is unlikely to lead to increased systemic adverse events due to VEGF inhibition. This prediction was confirmed in the clinical studies. Consequently, no dose adjustment appears to be required in patients with renal impairment.

Evaluator Comment

This was good quality population PK study in patients with RVO. The submitted study satisfactorily met the relevant TGA-adopted guideline on reporting the results of population PK analyses.[8] The data showed that serum plasma concentrations were similar in both AMD and RVO patients when plotted against corresponding dosing time points. However, there were only about half the number of serum ranibizumab samples in patients with AMD (383 samples) compared with patients with RVO (814 samples). The best overlap of serum plasma concentrations was demonstrated at Day 7 following the first dose. The data also showed that the majority of observed serum plasma concentrations following the 0.3 and 0.5 mg doses in patients with RVO were enclosed within the predicted 90% confidence intervals (CI) based on the AMD population PK model. Overall, the data suggest that PKs of ranibizumab following 0.3 and 0.5 mg doses are similar in patients with RVO and AMD.

The analysis of a number of baseline covariates showed that none had a statistically significant or clinically meaningful effect on ranibizumab transfer from the vitreous to the systemic circulation (that is, vitreous elimination), while CrCL was the only covariate to have a statistically significant effect on total apparent serum ranibizumab clearance following IVT injection. However, the sponsor has provided persuasive arguments suggesting that this statistically significant effect is unlikely to result in clinically meaningful changes in efficacy and safety in patients with RVO with impaired renal function treated with IVT ranibizumab. Overall, the covariate analysis demonstrated that no ranibizumab dosage adjustments based on the tested baseline patient covariates were required.

Pharmacodynamics

There were no new pharmacodynamic data provided.

Efficacy

Dosage selection for the pivotal studies

The two pivotal studies [BRAVO; CRUISE] both evaluated two doses of IVT ranibizumab to be administered at intervals of one month (0.3 mg and 0.5 mg) for 6 doses, followed by monthly doses “as needed” for a further 6 months. These two doses have been approved for the treatment of neovascular (wet) age-related macular degeneration (AMD) and are considered to be efficacious and safe for this condition. The sponsor selected the ranibizumab dosages for the two RVO pivotal studies based on the results observed in AMD.

Evaluator Comment

There were no formal dose ranging studies specifically for the treatment of RVO. The decision to use the same ranibizumab doses in RVO as used in the wet-AMD studies is considered to be a reasonable approach. The basic retinal pathology underlying both RVO and wet-AMD associated with excessive VGEF production resulting in increased permeability of the retinal vessels and leading to macular oedema and impaired visual acuity is considered to be sufficiently similar to support the decision to use the same ranibizumab doses for RVA as used for wet-AMD.

[8] EMEA. Committee for Medicinal Products for Human Use (CHMP), 21 June 2007. Guideline on Reporting the Results of Population Pharmacokinetics Analysis, CPMP/EWP/185990/06.

Pivotal efficacy studies

The submission included 2 pivotal studies of ranibizumab in patients with visual impairment due to macular oedema secondary to RVO [BRAVO; CRUISE]. In ***BRAVO***, visual impairment due to macular oedema secondary to BRVO was assessed while in ***CRUISE***, visual impairment due to macular oedema secondary to CRVO was assessed. Both studies were undertaken in the USA and in that country were sponsored by Genentech. In this AusPAR, both studies have been described together due to their similar design, methods and analysis. In both studies, patients were randomized to ranibizumab 0.3 mg, ranibizumab 0.5 mg or sham injection once monthly for 6 months (6 month treatment period), followed by monthly injections on an "as needed" basis for 6 months (6 month observation period). In both studies, the primary efficacy end point at the end of the 6 month treatment period was the mean change from baseline in beast corrected visual acuity (BCVA). The basic outlines of the 2 pivotal studies are summarised in Table 6. The 6 month treatment period data from ***BRAVO*** and ***CRUISE*** have been published (Campochiaro et al., 2010 and Brown et al., 2010, respectively).[9,10]

Table 6: Summary of the pivotal, sham controlled studies.

Study No.	Study objective, population	Randomized patients	Treatment duration	Dosage[a]	Primary efficacy endpoint[b]
FVF4165g BRAVO	Efficacy (superiority of ranibizumab to sham) and safety in patients with macular edema secondary to BRVO	397	6-month treatment period	1: Ranibizumab 0.3 mg 2: Ranibizumab 0.5 mg 3: Sham injection	Change from BL in BCVA at Month 6
			12 months (including 6-month observation period)	1: Ranibizumab 0.3 mg 2: Ranibizumab 0.5 mg	
FVF4166g CRUISE	Efficacy (superiority of ranibizumab to sham) and safety in patients with macular edema secondary to CRVO	392	6-month treatment period	1: Ranibizumab 0.3 mg 2: Ranibizumab 0.5 mg 3: Sham injection	Change from BL in BCVA at Month 6
			12 months (including 6-month observation period)	1: Ranibizumab 0.3 mg 2: Ranibizumab 0.5 mg	

BCVA=best corrected visual acuity; BL=Baseline; BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion.

[a] During the treatment period, patients received monthly injections of ranibizumab 0.3 mg, ranibizumab 0.5 mg, or sham injection. During the observation period, if a patient required treatment, patients randomly assigned to treatment with ranibizumab 0.3 mg were given ranibizumab 0.3 mg and patients randomly assigned to sham or ranibizumab 0.5 mg were given ranibizumab 0.5 mg.

[b] The primary efficacy endpoint was based on the treatment period (sham-controlled) data.

BRAVO (FVF4165g) and CRUISE (FVF4166g)

Study design, objectives, locations and dates

The two pivotal studies were both Phase III, multicentre, randomized, sham injection controlled studies of the efficacy and safety of ranibizumab IVT injections in subjects with macular oedema secondary to BRVO [**BRAVO**] or CRVO [**CRUISE**].

The primary objectives of both studies were:

- to evaluate the efficacy of IVT injections of ranibizumab administered monthly for 6 months for the improvement of visual acuity as measured by the mean change in best corrected visual acuity (BCVA) at 6 months compared with baseline; and

[9] Campochiaro PA, Heier JS, Feiner L et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary endpoint results of a Phase III study. Ophthalmology 2010; 117: 1124-1133.

[10] Brown DM, Campochiaro PA, Singh RP et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary endpoint results of a Phase III study. Ophthalmology 2010; 117: 1102-1112.

- to evaluate the safety and tolerability of IVT injections of ranibizumab administered monthly for 6 months, followed by a 6 month observation period during which protocol specified re-treatment criteria could trigger re-treatment at monthly intervals.

The secondary objectives of both studies were:

- to evaluate the efficacy of IVT injections of ranibizumab administered monthly for 6 months with respect to visual acuity outcomes, anatomic outcomes, and patient reported visual function outcomes; and
- to evaluate the pharmacokinetics of ranibizumab in subjects with RVO.

BRAVO was initiated on 9 July 2007 and completed on 2 November 2009. The sponsor's original *Clinical Study Report* (CSR) included the results for the 6 month treatment period and was dated 10 November 2009. The addendum CSR presented the results from the entire 12 month study period (including the results for the 6 month observation period) and was dated 30 July 2010. ***BRAVO*** was conducted at 93 sites in the USA.

CRUISE was initiated on 16 July 2007 and completed on 10 December 2009. The original CSR included the results for the 6 month treatment period and was dated 18 November 2009. The addendum CSR presented the results from the entire 12 month study period (including the results for the 6 month observational period) and was dated 16 August 2010. ***CRUISE*** was conducted at 95 sites in the USA.

Both studies consisted of a 28 day screening period (Days -28 to -1) and a 6 month treatment period (Day 0 and Months 1, 2, 3, 4, and 5), followed by a 6 month observation period (Month 6 through to completion of the study at Month 12). The duration of both studies was 12 months, excluding the 28 day screening period. During screening, the central reading centre (University of Wisconsin Fundus Photograph Reading Center [UWFPRC]), evaluated macular optical coherence tomography [OCT] images to determine subject eligibility. In both studies, eligible subjects were randomized 1:1:1 so that approximately 130 subjects in each of the three treatment groups received monthly treatment during the 6 month treatment period with the last treatment being given at Month 5. Only one eye was chosen as the study eye.

Inclusion and exclusion criteria

Both studies included subjects aged ≥ 18 years with macular oedema secondary to BRVO [BRAVO] or with macular oedema secondary to CRVO [CRUISE]. In both studies written informed consent was obtained and subjects were screened for eligibility before initiation of any study procedures. The inclusion criteria were similar for both studies. The inclusion and exclusion criteria were extensive but included the following ocular inclusion criteria (study eye):

Foveal centre – involved macular oedema secondary to BRVO [BRAVO] or CRVO [CRUISE]. Subjects were screened for enrolment at the time of diagnosis of BRVO or CRVO but no longer than 12 months after diagnosis.

In ***BRAVO,*** BRVO was defined as an eye that had retinal haemorrhage or other biomicroscopic evidence of RVO (for example, telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in one quadrant or less of the retina drained by the affected vein. Hemiretinal vein occlusion (HRVO) was defined as an eye that had retinal haemorrhage or other biomicroscopic evidence of RVO (for example, telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in more than one quadrant and up to three quadrants. Typically, an HRVO is an RVO that involves two altitudinal quadrants. For the purposes of this study, eyes with

HRVO were treated the same as eyes with BRVO. The presence of both BRVO and HRVO was assessed by fluorescein angiography.

In ***CRUISE***, CRVO was defined as an eye that had retinal haemorrhage or other biomicroscopic evidence of RVO (for example, telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in three quadrants or more of the retina drained by the affected vein. The presence of a CRVO was assessed by fluorescein angiography.

Other inclusion criteria included:

- *Both studies*, best corrected vision (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart of 20/40 to 20/400 (Snellen equivalent) in the study eye.
- *Both studies*, mean central subfield thickness ≥ 250 μm on two (OCT) measurements (at screening [confirmed by the central reading centre, UWFPRC] and Day 0 [confirmed by the evaluating physician]) in the study eye.
- *Both studies*, media clarity, pupillary dilation, and participant cooperation sufficient to obtain adequate fundus photographs.

Evaluator Comment

The exclusion criteria were extensive and included prior episodes of RVO. In effect, the studies involved patients with RVO uncomplicated by other significant ocular conditions resulting from the disease itself or other ocular diseases. The exclusion criteria included patients with ocular conditions which could confound the interpretation of the efficacy results (for example, ocular disease that may have been associated with increased intraocular VGEF levels). The studies excluded patients with a history of cerebral vascular accident or myocardial infarction within 3 months prior to Day 0 of the studies.

Study treatments

In *both studies*, during the 6 month treatment period, patients randomized to the ranibizumab treatment groups received IVT injections of ranibizumab (0.3 mg or 0.5 mg) in a single dose regimen given every month (Day 0 through to Month 5 visit), for a total of six injections. Patients were eligible for re-treatment with ranibizumab in the following 6 month observation period (Month 6 through to Month 11 visits) if they met protocol specified re-treatment criteria (see below). Patients randomized to ranibizumab groups could have received a maximum of 12 monthly injections of ranibizumab throughout the study (6 injections in the treatment period, followed by 6 injections in the re-treatment period if meeting re-treatment criteria at each monthly assessment visit). The protocol did not specify that the study drug was to be administered at any particular time of day or at any time relative to meals. Missed injections were not replaced.

In *both studies*, during the 6 month treatment period, patients randomized to receive sham treatment received sham injections in a single dose regimen given every month (Day 0 through the Month 5 visit), for a total of six sham injections. Patients were then eligible for re-treatment with 0.5 mg ranibizumab injections during the observation period (Month 6 through to Month 11) if they met the protocol specified re-treatment criteria (see below). Patients randomized to the sham group could have received a maximum of six sham injections and six ranibizumab 0.5 mg injections throughout the study. Missed injections were not replaced.

In *both studies*, after the 6 month treatment period, all patients continued to be monitored for safety and efficacy outcomes at each monthly visit up to and including Month 12. During the 6 month observation period (beginning at the Month 6 visit), all patients were

evaluated monthly to determine the need for re-treatment with ranibizumab with Month 11 being the last visit at which re-treatment could be given (a maximum of 6 re-treatments could be given). Patients randomized to the ranibizumab 0.3 mg group were re-treated with 0.3 mg if they qualified for re-treatment, and patients randomized to either the sham or the ranibizumab 0.5 mg group were re-treated with 0.5 mg if they qualified for re-treatment. The protocol specified *re-treatment criteria* in the study eye were:

- BCVA of 20/40 or worse (Snellen equivalent) using ETDRS charts; or
- Mean central subfield thickness ≥ 250 μm on OCT.

BRAVO (but not ***CRUISE***) included *criteria for rescue treatment with laser treatment.* In all three treatment groups in the 6 month treatment period, the evaluating physician determined the need for rescue laser treatment at the Month 3 visit using rescue criteria. If the criteria for rescue treatment with laser at the Month 3 visit were not met, re-evaluation was undertaken at subsequent monthly visits (Month 4 or 5) during the treatment period. Similarly, in all three treatment groups in the 6 month observation period, the evaluating physician determined the need for rescue laser treatment at the Month 9 visit using rescue criteria. If the rescue criteria at the Month 9 visit were not met, re-evaluation was undertaken at subsequent monthly visits (Month 10 or 11) during the observation period. The protocol specified rescue criteria were BCVA 20/40 or worse (Snellen equivalent) using ETDS charts or mean central subfield thickness ≥ 250 μm on OCT, **and** compared with the visit 3 months prior to the current visit, the BCVA gain was < 5 letters or there was a decrease of < 50 μm in mean central subfield thickness.

Evaluator Comment

Subjects receiving sham injections did not receive IVT injections of "placebo". This is justifiable as there are ethical concerns given the risk of infection with IVT injections. In sham treatment, the hub of the syringe (without the needle) was placed against the pre-anaesthetized conjunctival surface and the plunger was then slowly depressed with the aim being to mimic the action of an IVT injections. The re-treatment criteria were based on either a decrease in visual acuity **or** an increase in central retinal thickness. However, the proposed indication includes decreased visual acuity secondary to macular oedema but not macular oedema alone. Consequently, the re-treatment criteria are wider than the proposed indication. It is considered that that the re-treatment criteria should have included measures of both visual acuity and retinal thickness in order to align the criteria with the proposed indication (BCVA of 20/40 or worse [Snellen equivalent] using ETDRS charts **and** mean central subfield thickness ≥ 250 μm on OCT). *The sponsor should be requested to comment on the relationship between the re-treatment criteria and the proposed indication.*

Statistical considerations

In *both studies*, subjects were randomized to treatment groups by an interactive voice randomized system (IVRS). Prior to randomization on Day 0, OCT images at screening were reviewed for each subject by the central reading centre (UWFPRC) to obtain an objective assessment of eligibility. The BCVA and retinal thickness eligibility were required to be met during both the screening period (as confirmed by the central reading centre) and on Day 0 (as determined by the evaluating physician). Site personnel telephoned the IVRS on Day 0 to randomize the subject, after confirmation of eligibility requirements

Randomization was stratified by Day 0 BCVA score (≤ 34 letters [approximately worse than 20/200] vs 35–54 letters [approximately 20/200 to worse than 20/80] vs ≥ 55 letters [approximately 20/80 or better]) based on the ETDRS chart and assessment at a

starting test distance of 4 metres and by study centre. A dynamic randomization method was used to obtain an approximately 1:1:1 ratio between the three treatment groups, and to achieve balance within each treatment group defined by VA score, and balance within each study centre between the three treatment groups. A biased coin assignment was used when the imbalance within a stratum exceeded a specified threshold.

In order to meet the *masking requirements of both studies*, a minimum of two investigators per study site was required. At least one investigator was designated as the evaluating physician, who was masked to treatment assignment and evaluated all ocular assessments. At least one other investigator (and designated assistants, as needed) was designated as the injecting physician, who was unmasked to treatment assignment and performed the study drug injections (ranibizumab or sham) but was masked to the dose of study drug (0.3 mg vs 0.5 mg). Treatment was masked for at least 6 months and all study subjects remained masked to their treatment assignment throughout the study.

Evaluator Comment

The randomization method was satisfactory. Stratification based on visual acuity was a satisfactory method of accounting for possible confounding due to differences in visual acuity in the randomized treatment groups. Central foveal thickness, assessed with OCT, was evaluated in a central reading unit by certified assessors using standardized protocols. These procedures should have minimized the potential for observer bias based on interpretation of OTC readings. Overall, masking procedures appeared to have been satisfactory. However, it was stated that patients were prescribed post-injection, self administered antimicrobials but it was not explicitly stated whether patients randomized to sham treatment were prescribed self administered "post-injection" antimicrobials or placebo. If sham treated patients were not prescribed self administered "post-injection" medication (antimicrobials or placebo) then it is not possible to state that patients in the studies were completely masked to the treatment received. *The sponsor should be requested to clarify whether patients in the sham treatment group received prescribed "post–injection" medications.*

Primary efficacy population

The statistical methods outlined below were the same for both pivotal studies. Efficacy endpoints were analysed in the "intention to treat" (ITT) population, with patients grouped according to the treatment assigned at randomization. The ITT population was the primary population used in the efficacy analyses. For all primary and secondary 6 month treatment period efficacy endpoints, missing values were imputed using the last observation carried forward (LOCF) method. All statistical tests were two-sided. In addition to p-values for statistical tests, estimates and CIs were provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment group and the difference in means or proportions between two treatment groups were calculated. All CIs were two sided and at the 95% level.

Primary efficacy outcome analysis 6 month treatment period

The primary efficacy outcome of mean change from baseline in BCVA at 6 months was compared between each ranibizumab group and the sham injection (control) group using an analysis of variance (ANOVA) model stratified by baseline BCVA score in the study eye (≤ 34, 35−54, ≥ 55 letters), with no additional covariate adjustment. The Hochberg−Bonferroni multiple comparison procedure was used to adjust for comparisons of the two ranibizumab groups with the sham injection control group in order to maintain an overall type I error rate of 0.05. If the p-values for both comparisons were ≤ 0.05, both ranibizumab groups were considered statistically significantly different from the sham group. If the p-value for the comparison of one ranibizumab group with the sham group

was > 0.05, the other ranibizumab group was considered statistically significantly different from the sham group only if the p-value for its comparison with the sham group was ≤ 0.05/2 (≤ 0.025).

Secondary efficacy outcome analyses 6 month treatment period

The following *secondary efficacy outcomes* at 6 months were compared between each ranibizumab group and the sham injection group using the Cochran-Mantel-Haenszel (CMH) Chi-squared test stratified by baseline BCVA score in the study eye (≤ 34, 35−54, ≥ 55 letters): the proportion of patients who gained ≥ 15 or lost < 15 letters in BCVA score compared with baseline; and the proportion of patients with a central foveal thickness of ≤ 250 μm. The *following secondary efficacy outcomes* over time up to 6 months were compared between each ranibizumab group and the sham injection group using an ANOVA or analysis of covariance (ANCOVA) model: mean change from baseline in BCVA score; mean absolute change from baseline in central foveal thickness assessed on OCT; and mean change from baseline in the NEI VFQ-25 near and distance activities subscales. Statistical analyses of the secondary endpoints included pre-specified type I error management plans to account for multiple comparisons.

Supportive sensitivity analyses 6 month treatment period

Supportive sensitivity analyses were undertaken on the primary efficacy endpoint and the two secondary efficacy endpoints relating to the proportion of patients who gained ≥ 15 or lost < 15 letters in BCVA score. The sensitivity analyses for these three endpoints included unstratified analyses in the ITT LOCF population and stratified and unstratified analyses in the ITT observed data population (that is, without imputation of missing values) and "per protocol" observed data population. In addition, for the two secondary endpoints relating to the proportion of patients who gained ≥ 15 or lost < 15 letters in BCVA score sensitivity analyses were undertaken in the ITT population with worst-outcome imputation. Furthermore, for all efficacy endpoints (except for the endpoint of proportion of patients who required scatter photocoagulation in the study eye at or prior to 6 months), analyses based on observed data, with no imputation of missing data, were performed as supportive analyses.

Subgroup analyses – 6 month treatment period

The Statistical Analysis Plan (SAP) also included a number of pre-specified subgroup analyses of the primary efficacy endpoint and the two secondary efficacy endpoints relating to the proportion of patients who gained ≥ 15 or lost < 15 letters in BCVA score. These subgroup analyses included age (< 65 years, ≥ 65 years), sex (male, female), race (White, non-White), BCVA score in the study eye (≤ 34, 35 to 54, ≥ 55 letters), foveal thickness as assessed on OCT in the study eye (< 450 μm, ≥ 450 μm) and any prior therapies for RVO in the study eye (yes, no). For each subgroup, the difference in means or proportions between the active treatment groups and the control group and a CI for the difference were calculated. Missing BCVA scores were imputed using the LOCF method. Patients with missing demographic and baseline values used to define the subgroups were excluded from the respective subgroup analyses.

Secondary efficacy endpoints 6 month observation period

During the 6 month observation period, all patients were eligible to receive monthly retreatment with IVT injections of ranibizumab if they meet the re-treatment criteria. Therefore, efficacy analyses based on the 6 month observation period data did not involve formal comparisons between treatment groups and was based on descriptive statistics only. The primary analyses of efficacy endpoints for the observation period were based on the ITT population and missing values were imputed using the LOCF method. Supportive

analyses were based on observed data with no imputation of missing data. Efficacy data from the observation period were summarized separately for the group of patients initially in the sham injection group and eligible to receive treatment with ranibizumab during the 6 month observation period. Descriptive summaries of changes in key efficacy outcomes from month 6 and from the time of first dosing were performed. In addition, the number of patients completing the study overall was tabulated by treatment group. The total number of injections per subject, the number of laser rescue treatments received [BRAVO], the laser rescue criteria met [BRAVO] and the ranibizumab re-treatment criteria met during the observation period were tabulated by treatment group.

Timing of analyses

The analysis of data from the 6 month treatment period was performed when all patients had either completed the Month 6 visit or had discontinued before this visit. Treatment assignment was unmasked to the personnel performing the analysis when all data through to Month 6 were in the database and the data had been cleaned and verified. The analysis of complete data for the study, including data from the 6 month observation period, was performed when all patients had either completed the visit at Month 12 or had discontinued before this visit and all data were in the database. Patients, study site personnel (with the exception of the injecting physician and assistant, if needed), and the central reading unit personnel remained masked to individual treatment assignments until after the study was completed, the database locked, and the study analyses finalized.

Evaluator Comment

The statistical methods were considered to be satisfactory. The described methods are standard and appropriate for the analyses of the various primary and secondary efficacy endpoints at the end of 6 month treatment period. The ITT-LOCF population was the primary population used in the efficacy analyses and this is a conventional and accepted population for pivotal efficacy study analyses. The per protocol (PP) population included randomized patients who were considered to be sufficiently compliant with the protocol according to pre-specified criteria. These criteria have been examined and are considered to be appropriate. The PP population was used in supportive sensitivity analyses of the primary efficacy endpoint and for the 6 month efficacy endpoints based on visual acuity.

The statistical methods included pre-specified and acceptable methods to account for multiplicity of testing of both the primary and secondary endpoints. The methods used for the secondary endpoints were comprehensively described in the SAP and included the Hochberg-Bonferroni procedure and hierarchical testing procedures to control the type 1 error rate at 0.05. The SAP included a number of pre-specified subgroup analyses which are considered to be primarily exploratory. Both studies included a number of pre-specified exploratory analyses. These analyses have not been discussed in this report as it is considered that they are not directly relevant to the determination of efficacy for the purposes of this evaluation. The 6 month observational data were analysed using descriptive methods only. This is appropriate as the treatment groups might not have been comparable due to different re-treatment uptake among the three groups. In addition to the ITT and PP populations, the studies also included safety evaluable populations which will be defined later in this report.

In BRAVO, statistical analysis of the proportion of patients with a BCVA Snellen equivalent of 20/200 or worse at 6 months appeared to be low and the proportion of patients who lost < 15 letters in BCVA score at Month 6 compared with baseline appeared to be high. Consequently, the SAP was amended with the analysis method for these two endpoints being changed from large sample methods (CMH Chi-squared) to exact methods (Fisher's exact test and exact tests for CIs). The SAP for both BRAVO and CRUISE specified that

efficacy data from the observation period were to be summarized separately for the sham/0.5 mg group, with descriptive summaries of changes in key efficacy outcomes from Month 6 and from the time of first ranibizumab dosing to be performed. However, as the majority of the patients in the sham/0.5 mg group were dosed with ranibizumab at Month 6, only descriptive summaries of changes in key efficacy outcomes from Month 6 were tabulated.

Sample size

In *both studies*, sample size was determined on the basis of the primary efficacy endpoint. A sample size of 390 subjects (130 subjects per treatment group) provided 90% power in the ITT analysis to detect a statistically significant difference between one or both ranibizumab groups and the sham group in mean change from baseline in BCVA score at 6 months, assuming a mean change of +8, +6, and –2 letters [CRUISE] or +12, +10, and +2 [BRAVO] from baseline in BCVA score at 6 months for the 0.5 mg, 0.3 mg and sham treated subjects, respectively, and assuming an SD for the change from baseline in BCVA score at 6 months of 20 letters for each of the ranibizumab groups and 28 letters for the sham group. Calculations were based on a 1:1:1 randomization ratio, a two-sided test for equality of means using a normal approximation and assuming unequal variances (for comparison of each ranibizumab group with the sham group) and the Hochberg–Bonferroni multiple comparison procedure at an overall α level of 0.05.

Evaluator Comment

The proposed sham subtracted mean change from baseline in both studies was +10 letters for ranibizumab 0.5 mg and +8 letters for ranibizumab 0.3 mg. Consequently, it can be inferred that these differences are the minimal clinically significant improvements in BCVA scores for the two ranibizumab doses. In BRAVO, the assumption was that there would be a small increase from baseline in the BCVA score in the placebo group (+2 letters), while in CRUISE the assumption was that there would be a small decrease in the BCVA score in the placebo group (-2 letters). The assumed differences in the placebo groups reflects the different natural history over 6 months of BRVO (potential improvement) and CRVO (progression) and were considered to be acceptable.

Efficacy variables and outcomes

Primary efficacy outcome 6 month treatment period

In *both studies* the primary efficacy outcome was the mean change from baseline in BCVA score at 6 months in the study eye. BCVA was measured in the study eye using the EDTRS visual activity chart assessed at distance of 4 metres.

Secondary efficacy outcomes 6 month treatment period

In *both studies* the secondary efficacy outcomes at 6 months in the study eye were:

- Proportion of subjects who gained ≥ 15 letters in BCVA score at 6 months compared with baseline.
- Proportion of subjects who lost < 15 letters in BCVA score at 6 months compared with baseline.
- Mean change from baseline in BCVA score over time up to 6 months.
- Proportion of subjects with a central foveal thickness of ≤ 250 μm, assessed on OCT, at 6 months.
- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 6 months.

- Mean change from baseline in the National Eye Institute Visual Function Questionnaire-25 [NEI VFQ-25] near activities subscale over time up to 6 months. The score could range from 0 to 100 with a higher score representing better functioning.
- Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 6 months. The score could range from 0 to 100 with a higher score representing better functioning.

Secondary efficacy outcomes at 12 months

In *both studies*, the secondary efficacy outcomes in the study eye for the 6 month observation period were:

- Mean change from baseline in BCVA score over time up to 12 months.
- Proportion of subjects who gained at least 15 letters in BCVA score at 12 months compared with baseline.
- Proportion of subjects who lost fewer than 15 letters in BCVA score at 12 months compared with baseline.
- Proportion of subjects with a central foveal thickness of ≤ 250 μm, assessed on OCT, at 12 months.
- Mean absolute change from baseline in central foveal thickness, assessed on OCT, over time up to 12 months.
- Mean change from baseline in the NEI VFQ-25 near activities subscale over time up to 12 months.
- Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 12 months.

Evaluator Comment

The primary and secondary outcomes were considered to be satisfactory. Visual acuity is a well established and validated measure of visual function in retinal disease. The NEI VFQ-25 is an accepted method of assessing patient reported visual function. It assesses patient reported benefits and includes 12 subscales on general health, general vision, ocular pain, near activities, distance activities, social function, mental health, role difficulties, dependency, driving, colour vision and peripheral vision. In this study effect of visual impairment on the subscales of near and distant activities were assessed. The EDTRS visual acuity chart was used in the wet AMD studies, as was the NEI VFQ-25. OTC is now a standard tool used to measure retinal thickness in clinical trials of retinal disease.

Patient disposition

In both ***BRAVO*** and ***CRUISE***, 6 month completion rates in the total population were high (94.7% [n=376] and 92.6% [n=363], respectively), as were the 12 month completion rates (89.7% [n=356] and 89.0% [n=349], respectively). In *both studies*, discontinuations due to adverse events prior to 6 months were < 4% in each of the treatment groups and the cumulative rates for discontinuation due to adverse events prior to 12 months were < 5% in each of the three treatment groups.

In ***BRAVO,*** the number of patients randomized to the sham, ranibizumab 0.3 mg and ranibizumab 0.5 mg treatment groups was 132, 134 and 131, respectively. There was one patient randomized to the sham group and one to the 0.5 mg group who did not receive any study drug during the study. The respective percentage of patients in each treatment

group completing the study through to Month 6 was 93.2%, 95.5% and 95.4%, and through to Month 12 was 86.4%, 88.8% and 93.9%.

In ***CRUISE***, the number of patients randomized to the sham, ranibizumab 0.3 mg and ranibizumab 0.5 mg treatment groups was 130, 132 and 130, respectively. There was one patient randomized to the sham group and one to the 0.5 mg group who did not receive any study drug during the study. The respective percentage of patients in each treatment group completing the study through to Month 6 was 88.5%, 97.9% and 91.5% and through to Month 12 was 83.8%, 95.5% and 87.8%.

In ***BRAVO***, during the 6 month observation period the average number of ranibizumab injections received per patient (of 6 possible injections) was higher in those who had been treated with sham injections during the 5 month treatment period (3.6 injections) than in those who had been treated with ranibizumab injections (2.8 and 2.7 injections for the 0.3 mg and 0.5 mg groups, respectively). In addition, 78.8% of all patients randomized to the sham group compared with 41.0% and 38.2% of all subjects randomized to the 0.3 mg and 0.5 mg groups, respectively, received their first injection of ranibizumab during the observation period at Month 6.

In ***CRUISE***, during the 6 month observation period the average number of ranibizumab injections received per patient (of 6 possible injections) was 3.7 injections for the patients who had been treated with sham injections during the 6 month treatment period and 3.8 and 3.3 injections for the patients who had been treated with ranibizumab injections (0.3 mg and 0.5 mg, respectively). In addition, 76.9% of all patients randomized to the sham group compared with 56.1% and 49.2% of all patients randomized to the 0.3 mg and 0.5 mg groups, respectively, received their first injection of ranibizumab during the observation period at Month 6

In ***BRAVO***, of the 397 randomized patients 13.4% (n=53) failed to meet at least one inclusion or exclusion criteria, with similar rates being reported across the three treatment groups. Overall, the most common exclusion criterion not met was improvement of > 10 letters on BCVA between screening and Day 0. This was reported in 4.3% (n=17) of patients overall: 6.1% (n=8), 3.7% (n=5), and 3.1% (n=4) in the sham, ranibizumab 0.3 mg and ranibizumab 0.5 mg treatment groups, respectively.

In ***BRAVO***, major protocol deviations during the 12 month study period occurred in 23.5% (n=31), 24.6% (n=33) and 29.0% (n=38) of randomized patients in the sham/0.5 mg, ranibizumab 0.3 mg and ranibizumab 0.5 mg groups, respectively. Missed study drug treatments, violation of study eligibility criteria not approved by the sponsor and missing visual acuity score at baseline or Month 6 were the most common deviations. Dosing errors occurred in 2 patients (1 in a patient randomized to the 0.5 mg group but given 0.3 mg at Month 4 [assigned to the 0.5 mg group for the efficacy and safety analyses]; and 1 in a patient randomized to the sham group who was re-treated at Month 6 with sham rather than 0.5 mg [assigned to sham/0.5 mg group for the efficacy and safety analyses]). Treatment assignments were unmasked in 9 patients: 3 were unmasked by the sponsor for safety reporting; and 6 were inadvertently unmasked at the study sites.

In ***CRUISE***, of the 392 randomized patients, 8.7% (n=34) failed to meet at least one inclusion or exclusion criteria, with the failure rate in the ranibizumab 0.3 mg group (6.1% [n=6]) being lower than in the sham (10.8% [n=14]) and ranibizumab 0.5 mg group (9.2% [n=12]) groups. Overall, the most common exclusion criterion not met was improvement of > 10 letters on BCVA between screening and Day 0. This was reported in 3.1% (n=12) of patients overall: 3.8% (n=5), 2.3% (n=3), and 3.1% (n=4) in the sham/0.5 mg, ranibizumab 0.3 mg and ranibizumab 0.5 mg treatment groups, respectively.

In ***CRUISE***, major protocol deviations during the 12 month study period occurred in 32.3% (n=42), 22.7% (n=30) and 31.5% (n=41) of randomized patients in the sham/0.5 mg, ranibizumab 0.3 mg and ranibizumab 0.5 mg groups, respectively. Missed study drug treatments and missing VA scores for the study eye at baseline or Month 6, including those due to discontinuation from the study, were the most common deviations, with the sham/0.5 mg and 0.5 mg groups having higher rates than the 0.3 mg group. Treatment assignments were unmasked for 6 patients: 1 (0.5 mg group) was unmasked by the sponsor for safety reporting; and 5 were inadvertently unmasked at the study site.

Evaluator Comment

In both BRAVO and CRUISE, 6 and 12 month completion rates in the total population were high. The high completion rates support the robustness of the statistical analyses of the efficacy outcomes.

Baseline demographics and patient characteristics

In *both studies*, baseline demographics were similar in the three treatment groups. The mean ages of patients were 65.2 to 67.5 years in ***BRAVO*** ranging from 26 to 91 years and 65.4 to 69.7 years in ***CRUISE*** ranging from 20 to 91 years. In both studies, the greatest percentage of patients was in the 65 to < 85 years of age group in all treatment groups. In both studies, marginally more patients were male (53% to 57%) and the majority of patients were White (82% to 87%).

Baseline ocular characteristics in the study eye for both studies are summarised in Table 7. In both studies, VA was better in the fellow eye (non-study eye) compared with the study eye. In the fellow eye [BRAVO], randomized patients had a mean VA score of 79 to 81 letters at baseline (approximate Snellen equivalent, median 20/20) across all three treatment groups. In the fellow eye [CRUISE], randomized patients had a mean VA score of 79 to 80 letters at baseline (approximate Snellen equivalent, median of 20/20 to 20/25) across all three treatment groups.

Table 7: Pivotal studies – baseline ocular characteristics; randomized patients

	BRAVO			CRUISE		
Characteristic	Sham/0.5 mg (n = 132)	0.3 mg (n = 134)	0.5 mg (n = 131)	Sham/0.5 mg (n = 130)	0.3 mg (n = 132)	0.5 mg (n = 130)
Months since diagnosis						
Mean (SD)	3.7 (3.7)	3.6 (4.1)	3.3 (3.1)	2.9 (2.9)	3.6 (3.2)	3.3 (3.7)
Range	0.0−16.0	0.0−35.0	0.0−13.0	0.0–14.0	0.0–12.0	0.0–27.0
VA Score (letters 0-100)						
Mean (SD)	54.7 (12.2)	56.0 (12.1)	53.0 (12.5)	49.2 (14.7)	47.4 (14.8)	48.1 (14.6)
Range	16−73	25−73	22−79	16–71	9–72	21–73
≤ 34 letters	9 (6.8%)	9 (6.7%)	13 (9.9%)	26 (20.0%)	33 (25.0%)	30 (23.1%)
35-54 letters	50 (37.9%)	48 (35.8%)	49 (37.4%)	49 (37.7%)	46 (34.8%)	50 (38.5%)
≥ 55 letters	73 (55.3%)	77 (57.5%)	69 (52.7%)	55 (42.3%)	53 (40.2%)	50 (38.5%)
Approx Snellen equivalent						
Median	20/80	20/63−20/80	20/80	20/100	20/100	20/100
20/200 or worse	14 (10.6%)	14 (10.4%)	21 (16.0%)	35 (26.9%)	41 (31.1%)	39 (30.0%)
> 20/200 but < 20/40	99 (75.0%)	99 (73.9%)	95 (72.5%)	83 (63.8%)	82 (62.1%)	84 (64.6%)
20/40 or better	19 (14.4%)	21 (15.7%)	15 (11.5%)	12 (9.2%)	9 (6.8%)	7 (5.4%)

In ***BRAVO,*** the mean central subfield thickness was similar between treatment groups at baseline, but the mean central foveal thickness of the study eye was lower in the sham group (488.0 µm) compared with the 0.3 mg and 0.5 mg groups (522.1 µm and 551.7 µm, respectively). The mean total macular volume was similar across the three treatment groups. In ***CRUISE***, the mean central foveal thickness, mean central subfield thickness, and mean total macular volume of the study eye were similar across the three treatment groups.

In ***BRAVO*,** on the basis of centralized baseline assessments, 82% to 83% of patients had a BRVO and 12% to 13% of patients had a hemi-central RVO. The occlusion involved the superior half of the retina in 50% to 59% of patients in each treatment group and 24% to 26% of patients were identified as having definite collateral vessels present on the disc. The total area of retinal haemorrhage in the centre subfield was similar across the three treatment groups. In ***CRUISE***, on the basis of the centralized baseline assessment, 92% to 97% of the total number of patients had a CRVO (that is, all 4 quadrants involved). Definite collateral vessels were present on the disc in 32% to 36% of patients in each treatment group. The total area of retinal haemorrhage in the centre subfield was similar across the three treatment groups.

Both studies included a summary of targeted medical history focussing on those conditions relevant to RVO. In ***BRAVO,*** the most frequently reported condition in all patients was hypertension, (71.5%), followed by diabetes mellitus (18.1%) and open angle glaucoma (11.6%). Of all randomized patients, 7.3% had a history of myocardial infarction (MI), 3.3% had a history of an ischaemic cerebrovascular accident (CVA) and 0.8% had a history of haemorrhagic CVA. In ***CRUISE***, the most frequently reported condition in all patients was hypertension (70.7%), followed by diabetes mellitus (22.7%) and open angle glaucoma (13.8%). Of all randomized patients, 6.4% had a history of MI, 3.1% had a history of an ischaemic CVA and none had a history of haemorrhagic CVA.

In ***CRUISE,*** approximately 14% of all subjects had received prior therapy for RVO in the study eye: ~7% anti-VEGF treatment; ~5% triamcinolone; ~4% laser therapy; ~1% other medication. In ***BRAVO***, approximately 18% of all subjects had received prior therapy for RVO in the study eye: ~6% anti-VEGF treatment; ~6% triamcinolone; ~11% laser therapy. The prior treatments in the study eye in both studies are summarised in Table 8.

Table 8: Pivotal studies – prior therapy for RVO in the study eye; randomized patients

	BRAVO			CRUISE		
Therapy for RVO	Sham/0.5 mg (n = 132)	0.3 mg (n = 134)	0.5 mg (n = 131)	Sham/0.5 mg (n = 130)	0.3 mg (n = 132)	0.5 mg (n = 130)
Any prior RVO therapy	25 (18.9%)	25 (18.7%)	21 (16.0%)	17 (13.1%)	20 (15.2%)	16 (12.3%)
Anti-VEGF treatment	8 (6.1%)	10 (7.5%)	7 (5.3%)	9 (6.9%)	11 (8.3%)	8 (6.2%)
Triamcinolone	10 (7.6%)	5 (3.7%)	10 (7.6%)	5 (3.8%)	7 (5.3%)	7 (5.4%)
Medication, other	0	0	0	2 (1.5%)	2 (1.5%)	1 (0.8%)
Laser therapy	17 (12.9%)	14 (10.4%)	13 (9.9%)	3 (2.3%)	7 (5.3%)	4 (3.1%)

In ***BRAVO***, concomitant ocular medications were used in the screening period or 12 month treatment period by 34.8%, 41.0% and 38.9% of patients in the sham/0.5 mg, ranibizumab 0.3 mg and ranibizumab 0.5 mg groups, respectively. In ***CRUIS***E, concomitant ocular medications were used in the screening period or 12 month treatment period by 35.4%, 36.4% and 44.6% of patients in the sham/0.5 mg, ranibizumab 0.3 mg and ranibizumab 0.5 mg groups, respectively. In both ***BRAVO*** and ***CRUISE***, the most commonly

used ocular medications in the three treatment groups were anti-glaucoma agents (10.6% to 16.0% and 14.6% to 18.2%, respectively).

In *both studies*, nearly all patients used at least one concomitant non-ocular medication during the screening period of the 12 month study period. Various types of medication were used and there were no notable differences among the three treatment groups in both studies.

Evaluator Comment

Within both studies, baseline characteristics were similar across the three treatment groups. On average, baseline VA was worse in CRUISE than in BRAVO. The number of patients in both studies stated to have a prior episode of RVO was low (2 in BRAVO and 2 in CRUISE). However, the percentage of patients receiving prior treatment in the study eye for RVO was ~18% in BRAVO and ~ 14% in CRUISE. *The sponsor should be requested to comment on the apparent discrepancy between the number of patients stated to have not met the exclusion criteria of prior episode of RVO and the number of patients receiving prior treatment for RVO in the study eye.*

Results for the primary efficacy outcome – 6 month treatment period

The results for the primary efficacy endpoint of mean change from baseline in BCVA score at Month 6 in the study eye are summarised in Table 9. In ***BRAVO*** the average number of injections received per subject (of 6 scheduled injections) was 5.5 sham injections and 5.7 ranibizumab injections for both the 0.3 mg and 0.5 mg groups, and in ***CRUISE*** the corresponding figures were 5.4, 5.8 and 5.5 injections. In ***BRAVO***, laser rescue treatment was administered to 27 (20.1%) patients in the ranibizumab 0.3 mg group, 28 (21.4%) in the ranibizumab 0.5 mg group and 76 (57.6%) in the sham group. The sensitivity analysis of mean change from baseline in BCVA at Month 6 (observed data) in the PP population was consistent with the primary efficacy analysis in both studies.

Table 9: BRAVO (FVF4165g) and CRUISE (FVF4166g) – primary efficacy endpoint; randomized patients

	Study FVF4165g			Study FVF4166g		
		Ranibizumab			Ranibizumab	
	Sham n=132	0.3 mg n=134	0.5 mg n=131	Sham n=130	0.3 mg n=132	0.5 mg n=130
Change from Baseline in visual acuity at Month 6						
Number of letters change from Baseline						
Mean (SD)	7.3 (13.0)	16.6(11.0)	18.3(13.2)	0.8 (16.2)	12.7(15.9)	14.9(13.2)
95% CI for mean[a]	(5.1,9.5)	(14.7,18.5)	(16.0,20.6)	(−2.0,3.6)	(9.9,15.4)	(12.6,17.2)
Difference in LS means (vs sham)[b]		9.4	10.6		11.5	13.8
95% CI for difference[b]		(6.6,12.2)	(7.6,13.6)		(7.7,15.3)	(10.3,17.4)
p-value (vs sham)[b]		< 0.0001	< 0.0001		< 0.0001	< 0.0001

ANOVA = analysis of variance; CI = confidence interval; LS = least squares.
Note: The last-observation-carried-forward method was used to impute missing data.
[a] Derived from the t-distributions.
[b] Based on pairwise ANOVA models adjusted for Baseline visual acuity score (≤ 34, 35–54, ≥ 55 letters).

Evaluator Comment

In both studies, both ranibizumab doses improved BCVA to a statistically significantly greater extent than sham injections. Furthermore, in both studies the sham subtracted improvement in BCVA was > 10 letters for ranibizumab 0.5 mg and > 8 letters for ranibizumab 0.3 mg. These differences were greater than the estimated differences used

to determine the sample size and power of the studies. Consequently, the differences can be considered to be clinically significant. Data from the published literature suggests that for eyes with VA better than 20/100, a change in VA between two time points of ≥ 5 letters has a high probability of (~90% or greater) of being a real change in VA and not a difference due to chance, while for eyes with VA worse than 20/100, a change of ≥ 10 letters would be necessary for the same degree of reassurance [Beck et al., 2007].[11]

Results for the secondary efficacy outcomes – 6 month treatment period

Gain of ≥ 15 letters from baseline at Month 6

In ***BRAVO***, the proportion of patients gaining ≥ 15 letters in the sham, 0.3 mg and 0.5 mg groups was 28.8%, 55.2% and 61.1% and the differences between ranibizumab and sham were 26.8% ([95%CI: 15.6, 31.3]; p<0.0001) for 0.3 mg and 31.3% ([95%CI: 20.1, 42.6]; p<0.0001) for 0.5 mg. In ***CRUISE***, the corresponding results in the sham, 0.3 mg and 0.5 mg groups were 16.9%, 46.2% and 47.7%, and the differences between ranibizumab and sham were 29.3% ([95%CI: 18.8, 39.7]; p<0.0001) for 0.3 mg and 30.3% ([95%CI: 19.6, 40.9]; p<0.0001) for 0.5 mg.

Loss of < 15 letters from baseline at Month 6

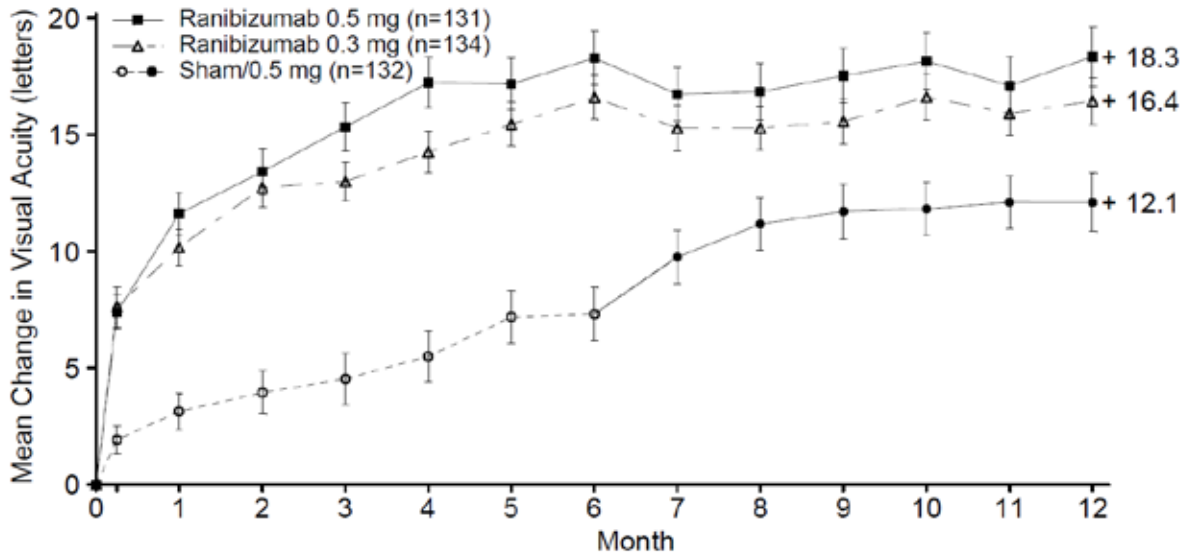
In ***BRAVO***, the proportion of patients losing < 15 letters in the sham, 0.3 mg and 0.5 mg groups was 95.5%, 100% and 98.5%, and the differences between ranibizumab and sham were 4.5% ([95%CI: 1.6, 9.9]; p=0.0141) for 0.3 mg and 3.0% ([95%CI: -1.5, 8.3]; p=0.2851) for 0.5 mg. In ***CRUISE***, the corresponding results in the sham, 0.3 mg and 0.5 mg groups were 84.6%, 96.2% and 98.5%, and the differences between ranibizumab and sham were 11.3% ([95%CI: 4.3, 18.2]; p=0.0019) for 0.3 mg and 13.6% ([95%CI: 7.2, 20.1]; p<0.0001) for 0.5 mg.

Differences in visual acuity over the 6 month treatment period [BRAVO]

In ***BRAVO***, a difference between each of the ranibizumab groups and the sham group in VA scores was observed as early as Day 7 after first treatment. On average, the VA score in the 0.3 mg and 0.5 mg groups had increased from baseline by 7.6 and 7.4 letters, respectively, at 7 days, by 10.2 and 11.6 letters, respectively, at 1 month, with further increases to 16.6 and 18.8 letters, respectively, at 6 months. In contrast, on average, the VA score in the sham group increased from baseline by 1.9 letters at 7 days, 3.1 letters at 1 month and 7.3 letters at 6 months. The change in VA over 12 months is summarised in Figure 3.

[11] Beck RW, Maguire MG, Bressler NM et al. Visual acuity as an outcome measure in clinical trials of retinal diseases. Ophthalmology 2007; 114: 804-1809.

Figure 3: BRAVO - Mean change from baseline in visual acuity score in the study eye; randomized subjects

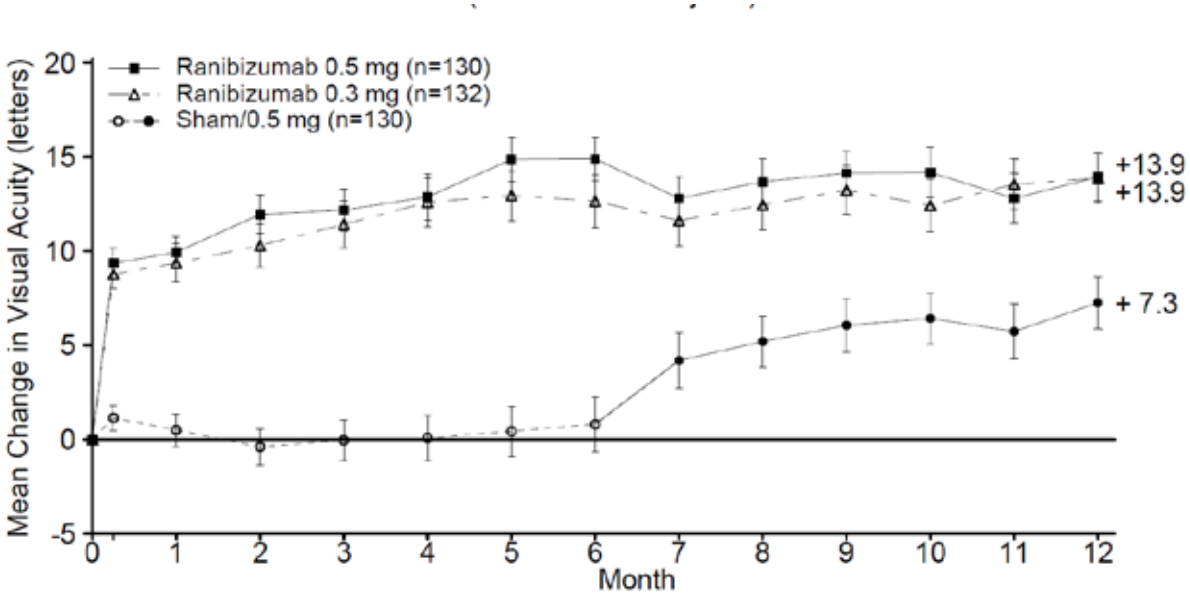


Note: The LOCF method was used to impute missing data. Vertical bars are ± 1 standard error of the mean.

Differences in visual acuity over the 6 month treatment period [CRUISE]

In ***CRUISE***, a difference between each of the ranibizumab groups and the sham group in VA scores was observed as early as Day 7. On average, the VA score in the 0.3 mg and 0.5 mg groups had increased from baseline by 8.8 and 9.3 letters, respectively, at 7 days, and by 9.4 and 9.9 letters, respectively, at 1 month, with further increases to 12.7 and 14.9 letters, respectively, at 6 months. In contrast, on average, the VA score in the sham group increased from baseline by 1.1 letters at 7, 0.5 letters at 1 month, and 0.8 letters at 6 months. The change in visual acuity over 12 months is summarised in Figure 4.

Figure 4: CRUISE - Mean change from baseline in visual acuity score in the study eye; randomized subjects



Note: The LOCF method was used to impute missing data. Vertical bars are ± 1 standard error of the mean.

Central foveal thickness ≤ 250 µm at Month 6

In ***BRAVO***, the proportion of patients with central foveal thickness ≤ 250 µm in the sham, 0.3 mg and 0.5 mg groups was 45.5%, 91.0% and 84.7%, and the differences between ranibizumab and sham were 45.5% ([95%CI: 36.0, 55.0]; p<0.0001) for 0.3 mg and 40.1% ([95%CI: 29.9, 50.2]; p<0.0001) for 0.5 mg. In ***CRUISE***, the corresponding results in the sham, 0.3 mg and 0.5 mg groups were 23.1%, 75.0% and 76.9%, and the differences between ranibizumab and sham were 51.9% ([95%CI: 41.6, 62.3]; p<0.0001) for 0.3 mg and 54.0% ([95%CI: 44.0, 64.1]; p< 0.0001) for 0.5 mg. The results for the percentage change from baseline in foveal thickness at Month 6 were consistent with those for the proportion of patients with central foveal thickness ≤ 250 µm at Month 6.

Change in central foveal thickness over the 6 month treatment period

In both studies, patients treated with both doses of ranibizumab had clinically meaningful reductions in mean central foveal thickness from Day 7 after the first injection through to Month 6. In addition in both studies, central foveal thickness decreased over the 6 month treatment period in the sham treatment groups.

Change in NEI VFQ-25 subscale scores at Month 6

The scores for both subscales could range from 0 to 100, with higher scores indicating better function. In both studies, scores for near and distance activities increased from baseline in all three treatments and the increases were statistically significantly superior for both 0.3 mg and 0.5 mg compared with placebo for all pairwise comparisons. For near activities scores, the differences between sham and 0.3 mg were 4.1 and 5.8, and between sham and 0.5 mg were 4.9 and 5.4. For distance activities scores, the difference between sham and 0.3 mg were 3.8 and 6.3, and between sham and 0.5 mg were 4.1 and 5.1.

Evaluator Comment

In both studies, the proportion of patients achieving a gain of ≥ 15 letters from baseline at Month 6 was statistically significantly greater with both doses of ranibizumab compared with sham (p<0.0001 for each pairwise comparison). In BRAVO, the proportion of patients achieving this outcome was about twofold higher with ranibizumab compared with sham and about threefold higher in CRUISE. In both studies, the proportion of patients losing < 15 letters was high in each of the three treatment groups, with the differences between ranibizumab and sham being greater in CRUISE (both pairwise comparisons statistically significant) than in BRAVO (only the pairwise comparison between sham and 0.3 mg being statistically significant). The proportion of patients in each treatment group losing < 15 letters was greater in BRAVO than in CRUISE, which reflects the difference in the natural history of BRVO and CVO. Both doses of ranibizumab also significantly reduced central foveal thickness compared with sham.

In both studies, greater increases in VA scores with both doses of ranibizumab compared with sham were observed as early at 7 days after the first treatment and were maintained throughout the 6 month treatment period. In BRAVO, improvement in VA scores occurred in the sham group over the 6 month treatment period in addition to both ranibizumab treatment groups. The improvement in the sham group in BRAVO may be attributed to a combination of factors including rescue laser treatment in 57.6% of patients in the sham group and the natural history of BRVO which includes spontaneous resolution in a subset of patients. In contrast, in CRUISE VA scores did not notably change over the 6 month treatment period in the sham group, while scores for both ranibizumab groups significantly increased. In both studies, the mean central foveal thickness decreased over the 6 month treatment period in both the ranibizumab groups and the sham group but to a greater degree in the ranibizumab groups.

In both studies, NEI-VFQ-25 self reported scores for near and distance activities increased from baseline in all three treatments and the increases were statistically significantly superior for both 0.3 mg and 0.5 mg compared with placebo for all pairwise comparisons. The differences between sham and ranibizumab scores were small on a scale which could range between 0-100. However, this are likely to be clinically meaningful as, on average, more patients self reported improvement in near and distance activities in the ranibizumab groups compared with the sham group.

Secondary efficacy outcomes – Month 12

During the 6 month observation period all patients were evaluated monthly and treated with ranibizumab if they met the protocol specified re-treatment criteria. The results for the secondary efficacy outcomes in both studies are reviewed below. In both studies, the protocol specified that the result would be summarised using descriptive statistics.

Change in BCVA score

In ***BRAVO***, at Month 12 the mean change from baseline in BCVA score (vs Month 6) for the sham, 0.3 mg and 0.5 mg groups was 12.1 (vs 7.3) letters, 16.4 (vs 16.6) letters and 18.3 (vs 18.3) letters, respectively. In ***CRUISE***, the corresponding results were 7.3 (vs 0.8) letters, 13.9 (vs 12.7) letters and 13.9 (vs 14.9 letters). In both studies, improvement in VA scores achieved at Month 6 in both the ranibizumab groups were maintained through to Month 12, while in the sham treatment groups further improvements were observed from Month 6 through to Month 12 (see Figures 3 and 4).

Gain of ≥ 15 letters in VA score

In ***BRAVO***, at Month 12 the proportion of subjects gaining ≥ 15 letters in VA score from baseline (vs Month 6) for the sham, 0.3 mg and 0.5 mg groups was 43.9% (28.8%), 56.0% (vs 55.3%) and 60.3% (vs 61.1%), respectively. In ***CRUISE***, the corresponding results were 33.1% (vs 16.9%), 47.0% (vs 46.2%) and 50.8% (vs 47.7%).

Loss of < 15 letters in VA score

In ***BRAVO***, at Month 12 the proportion of subjects losing < 15 letters in VA score from baseline (vs Month 6) for the sham, 0.3 mg and 0.5 mg groups was 93.9% (vs 95.5%), 99.3% vs 100% and 97.7% (vs 98.5%), respectively. In ***CRUISE***, the corresponding results were 90.0% (vs 84.6%), 96.2% (vs 96.2%) and 97.7% (vs 98.5%).

Decrease in central foveal thickness

In ***BRAVO***, at Month 12 the proportion of subjects with central foveal thickness of ≤ 250 µm (vs Month 6) for the sham, 0.3 mg and 0.5 mg groups was 78.8% (45.5%), 83.6% (vs 91.0%) and 86.3% (84.7%), respectively. In ***CRUISE***, the corresponding results were 70.8% (23.1%), 75.8% (vs 75.0%) and 77.7% (vs 76.9%).

Change in NEI VFQ-25 subscale scores (near and distance activities)

In both studies, there were no notable differences in changes from baseline in NEI VFQ-25 subscale scores for near and distance activities in the ranibizumab 0.3 mg and 0.5 mg groups at 12 months compared with 6 months.

Evaluator Comment

In both studies, increases in the BCVA score, proportion of patients achieving gains of ≥ 15 letters in VA score, proportion of patients with central foveal thickness ≤ 250 µm and improvements NEI FVQ-21 near and distance subscale scores at the end of the 6 month treatment period were maintained over the 6 month observation period in both ranibizumab dose groups. In addition, improvements in these four parameters from 6 to 12 months were also observed in patients initially randomized to sham and subsequently

treated with ranibizumab 0.5 mg in the 6 month observation period. The improvements in the sham groups are likely to be primarily attributable to treatment with ranibizumab 0.5 mg administered on a monthly "as needed" basis in the 6 month observation period. There was no control group in the 6 month observation period ("no ranibizumab" treatment group). Consequently, it is not possible to exclude spontaneous improvement in VA, retinal thickness and self reported visual function from Month 6 through to Month 12. Mean gain of ≥ 15 letters from baseline and/or mean loss of < 15 letters from baseline are considered to be clinically meaningful efficacy endpoints.

During the 6 month observation period all patients were eligible to receive ranibizumab injections (maximum of 6) on a monthly "as needed" basis if meeting the protocol specified re-treatment criteria. In BRAVO, the average number of ranibizumab injections received per patient in the 6 month observation period was higher in the sham group than in both the 0.3 mg and 0.5 mg groups (3.6, 2.8 and 2.7 injections, respectively). In CRUISE the average number of ranibizumab injections received per patient in the 6 month observation period was similar in the sham, 0.3 mg and 0.5 mg groups (3.7, 3.8 and 3.3 injections, respectively). In the two studies, the percentage of all randomized patients re-treated with ranibizumab during the observation period at Month 6 (first opportunity for re-treatment) was 78.8% [BRAVO] and 76.9% [CRUISE] in the sham/0.5 mg group, 41.0% [BRAVO] and 56.1% [CRUISE] in the 0.3 mg group, and 38.2% [BRAVO] and 49.2% [CRUISE] in the 0.5 mg group. In the 6 month observation period, the percentage of patients treated with ranibizumab prn was 87.1% [BRAVO] and 84.6% [CRUISE] in the sham/0.5 mg group, 79.1% [BRAVO] and 90.9% [CRUISE] in the 0.3 mg group, and 76.3% [BRAVO] and 84.4% [CRUISE] in the 0.5 mg group. In BRAVO, in the 12 month study period, rescue laser treatment to the study eye was administered to 61.4% (n=81) patients in the sham/0.5 mg group, 41.0% (n=55) in the 0.3 mg group, and 34.4% (n=45) in the 0.5 mg group.

Subgroup results – 6 month treatment period

The subgroup analyses for the primary endpoint of mean change from baseline in VA score at 6 months and for the secondary endpoint of proportion of patients who gained ≥ 15 letters in VA score at 6 months compared with baseline indicated that the results for the subgroup comparisons at 12 months were similar to those at 6 months.

Evaluator Comment

In both studies, the treatment effects of ranibizumab compared with sham for both visual acuity endpoints in the subgroups were consistent with the corresponding treatment effects in the total population. The following general observations can be made for the subgroup analyses of the primary efficacy endpoint in both studies: response was greater in patients aged < 65 years compared with patients aged ≥ 65 years; response in males and females was similar; response was similar in Whites and non-Whites; greater response was observed in subjects with better baseline VA; greater response was observed in patients with greater baseline central foveal thickness; and response was generally greater in patients with no prior therapy for RVO.

Analyses performed across trials

There were no analyses performed across trials. It was pre-specified that the efficacy data from the two pivotal studies would not be pooled because of the possibility that there might be differences in response to treatment between patients with BRVO and CRVO, and because of the use of laser rescue treatment in BRAVO. The decision not to pool the efficacy results from the two pivotal studies was acceptable for the reasons given by the sponsor.

Evaluator's conclusions on clinical efficacy

Both pivotal efficacy and safety studies were considered to be good quality clinical trials. In both studies, both doses of ranibizumab administered at monthly intervals for a total of 6 injections resulted in clinically and statistically significantly greater improvements in BCVA score at Month 6 compared with sham treatment. The improvement in BCVA score was greater in ***BRAVO*** than in ***CRUISE***, suggesting that treatment with ranibizumab might be more effective in patients with BRVO rather than CRVO. However, the greater improvement BCVA in ***BRAVO*** might be attributable to the availability of laser rescue treatment from the Month 3 visit in the 6 month treatment period and the potential for spontaneous improvement in a subset of patients with BRVO. In both studies, BCVA scores in both ranibizumab treatment groups were greater than in the sham treatment group as early as Day 7 after the first injection.

In both studies, the pre-specified secondary efficacy outcomes in the 6 month treatment period of proportion of patients gaining ≥ 15 letters from baseline, proportion of patients achieving central fovea thickness ≤ 250 µm at 6 months and mean change in NEI VFQ-25 subscales for near and distance activities all clinically and statistically significantly favoured both ranibizumab doses compared with sham treatment. However, the proportion of patients losing < 15 letters from baseline was high in all three treatment groups in both studies and statistically significantly favoured both doses of ranibizumab compared with sham treatment for all comparisons, except for the comparison between ranibizumab 0.3 mg and sham in *BRAVO.*

In both studies, during the 6 month observation period patients could be re-treated with ranibizumab at monthly intervals to a maximum of 6 doses if protocol specified criteria were met. Patients who had been randomized to sham treatment could be re-treated with ranibizumab 0.5 mg in the 6 month observation period if meeting the re-treatment criteria. The average number of ranibizumab 0.5 mg injections received by patients in the sham treatment groups was 3.6 in ***BRAVO*** (on average about 1 more injection than subjects in the ranibizumab groups) and 3.7 in ***CRUISE*** (on average about the same number of injections as subjects in the ranibizumab groups). In both studies, improvements in VA, central foveal thickness and NEI VFQ-25 subscale scores (near and distance activities) observed at Month 6 in the ranibizumab 0.3 mg and 0.6 mg treatment groups were maintained at Month 12. The Month 12 VA, central foveal thickness and self reported visual function outcomes for the sham/0.5 mg group were superior to those for the sham group at Month 6 (most probably due to the addition of ranibizumab in the 6 month observation period).

No conclusions can be made about the efficacy of ranibizumab beyond 12 months as the submission included no data beyond this time point. In addition, the absence of a "no ranibizumab" control group beyond 6 months limits the interpretation of the Month 12 ranibizumab efficacy data. Furthermore, the ranibizumab re-treatment criteria in the 6 month observational period were decreased VA **or** increased central retinal thickness which differed from the inclusion criteria which required both decreased VA **and** increased retinal thickness. Consequently, it is possible that beneficial outcomes in the 6 month observational period might be inflated due to re-treatment of patients with less severe disease than was required to enter the study. This is relevant as the proposed indication requires both decreased VA and macular oedema. No comparative analyses could be identified in the submission of the 12 month efficacy outcomes in patients re-treated in the 6 month observation period due to decreased VA only, increased retinal thickness only, or both decreased VA and increased retinal thickness

There was no systematic evaluation of the effects of ranibizumab withdrawal or rebound. However, once a patient had stopped treatment for the first time, the median duration of

the first disease free interval was 1 month (that is, re-treatment criteria not met in the 6 month observation period).

There were no data in patients with BRVO comparing laser therapy with ranibizumab. Laser therapy is generally considered to be standard treatment for this condition. In ***BRAVO*****,** laser rescue treatment was administered to 27 (20.1%) patients in the ranibizumab 0.3 mg group, 28 (21.4%) in the ranibizumab 0.5 mg group and 76 (57.6%) in the sham group during the 6 month treatment period (beginning at Month 3), and the corresponding figures in the 6 month observation period (beginning at Month 3 [Month 9 of the study]) were 41 (30.6%), 31 (23.7%) and 31 (23.5%) patients. At least one laser treatment during the 12 month study period was received by 81 (61.4%), 55 (41.0%) and 45 (34.4%) patients in the sham/0.5 mg, ranibizumab 0.3 mg and ranibizumab 0.5 mg treatment groups, respectively.

Overall, laser rescue therapy was commonly used in ***BRAVO*** and to some extent confounds the interpretation of the efficacy data. However, in the 6 month treatment period about threefold more patients in the sham group were treated with rescue laser therapy than in both ranibizumab groups. In addition, at Month 3 of the treatment period (after the third injection and before laser therapy) the mean (SD) increase in VA (letters) from baseline was 4.5 (12.5), 13.0 (9.6) and 15.3 (11.8) for the sham, 0.3 mg and 0.5 mg groups, respectively, with the difference between 0.3 mg and sham being 8.5 letters ([95%CI: 5.8. 11.1]; p<0.0001) and between 0.5 mg and sham being 10.8 letters ([95%CI: 7.8, 13.8]; p<0.0001). Consequently, the lower rates of administered laser therapy in the ranibizumab groups compared with the sham group in the 6 month treatment period and the clinically and statistically significantly greater increases in VA at Month 3 in both the ranibizumab groups compared with the sham group strongly suggest that ranibizumab treatment has a beneficial effect on BRVO unrelated to laser therapy.

Overall, the results demonstrated a clinically meaningful and statistically significant effect of ranibizumab 0.3 mg and 0.5 mg on VA, anatomical outcomes, and patient reported near and distance visual function at 6 months compared with sham treatment in patients with BRVO or CRVO. In addition, the beneficial effects observed with both doses of ranibizumab were maintained through to 12 months after initiation of treatment. While both doses of ranibizumab were efficacious, the results for the 0.5 mg dose were generally numerically superior to those for the 0.3 mg dose but the differences were relatively small. Neither of the two pivotal studies included statistical analyses of the efficacy outcomes comparing the two ranibizumab doses. It was considered that the efficacy data support the approval of the 0.5 mg dose for the treatment of patients with RVO.

It was proposed that ranibizumab 0.5 mg be administered monthly until maximum VA is achieved confirmed by stable VA for three consecutive monthly visits while on treatment. The submission included an exploratory analysis to test this proposal. In this analysis, VA was determined to be stable when changes between the minimum and maximum values over the last three assessments (including the current assessment) were within a margin of 3 letters (that is, VA max – VA min ≤ 3 letters). The VA stability criterion up to Month 6 was achieved by 58.9% (156/265) of pooled ranibizumab treated patients in ***BRAVO*** and 52.7% (138/262) of pooled ranibizumab treated patients in ***CRUISE***. The results from both studies indicated that meaningful VA stability was first reached in patients in the pooled ranibizumab group at Month 3 (after the third injection). In both studies, the results for the ranibizumab 0.5 mg group were consistent with those for the pooled ranibizumab group.

It was proposed that treatment with ranibizumab 0.5 mg be interrupted once VA has been stable for the three consecutive monthly assessments. The submission also included an exploratory analysis to test this proposal. In this analysis, the mean (SD) average change in

VA at 1 month after an injection administered when VA stability was first achieved was +0.8 (4.6) letters in ***BRAVO*** and 1.5 (4.2) letters in ***CRUISE*** in the pooled ranibizumab groups (that is, stability defined as VA values max – min ≤ 3 letters for 3 consecutive monthly visits with treatment at the first 2 visits). This analysis suggests that, on average, no further clinically meaningful improvement occurs in patients who have achieved stability over three consecutive monthly assessments who continue treatment. In both studies, the results for the ranibizumab 0.5 mg group were consistent with those for the pooled ranibizumab group.

It was proposed that treatment be reinitiated with 0.5 mg when disease stability is no longer observed due to deterioration of VA. The submission also included an exploratory analysis to test this proposal. In this analysis, change from retreatment to 1 month post retreatment was examined in both ***BRAVO*** and ***CRUISE*** in patients for whom VA loss was > 3 letters or ≤ 3 letters. In ***BRAVO***, in the pooled ranibizumab group (n=133) the average gain in BCVA in 85 patients with VA loss > 3 letters (VA stability lost) was 7.1 letters, compared with an average loss of 0.6 letters in 48 patients with VA loss ≤ 3 letters (VA stable). In ***CRUISE***, in the pooled ranibizumab group (n=132) the average gain in BCVA in 96 patients with VA loss > 3 letters (VA stability lost) was 9.3 letters, compared with the average gain of 2.9 letters in 33 patients with VA loss ≤ 3 letters. In both studies, the results for the ranibizumab 0.5 mg group were consistent with those for the pooled ranibizumab group. Overall, the results suggest that retreatment in patients who lose VA stability will, on average, result in meaningful improvement in VA at 1 month following the first re-treatment injection while, on average, in patients who are stable will result in no meaningful improvement in VA at 1 month following the first re-treatment injection.

The proposed treatment regimen is different from that used in the two pivotal studies which involved all patients being treated with 6 injections of ranibizumab at monthly intervals (0, 1, 2, 3, 4 and 5 months) with further treatment being determined by re-treatment criteria between Months 6 and 11. In both studies, improvement in BCVA at 3 months was about 12 to 15 letters in the ranibizumab 0.5 mg group compared with a change of about 0 to 4 letters in the sham group. These results provide support for the proposed treatment regimen. Overall, the efficacy over time data from ***BRAVO*** and ***CRUISE*** and the exploratory analyses data from the two studies relating to stability and re-treatment suggest that treatment should be initiated with at least 3 consecutive monthly injections of ranibizumab 0.5 mg and monthly injections should continue until maximum improvement in VA has been achieved. Consideration should be given to discontinuing treatment once improvement in VA has been achieved and maintained for three consecutive monthly assessments. Consideration should be given to re-treatment if the achieved VA stability is lost. However, if no improvement in VA has been achieved after the initial 3 consecutive monthly injections consideration should then be given to stopping ranibizumab treatment.

The number of monthly injections required to achieve and then maintain improvement in VA is likely to be highly variable in the patient population for whom ranibizumab will be used and will be dependent on the applied VA stability criteria. No VA improvement, stability or loss of stability criteria have been specified in the PI. Consequently, it is likely that these criteria might differ among treating clinicians and consideration could be given to specifying such VA criteria in the PI. However, it was considered that the preferable option is to leave decisions about continuing, discontinuing and retreating to individual clinicians based on the clinical condition and response to treatment of their individual patients.

Safety

Studies providing evaluable data

The safety profile of ranibizumab was based on data from the two, pivotal, Phase III efficacy and safety studies. The submission included a pooled summary of the safety data from these two studies. In these two studies the safety outcomes assessed were ocular and non-ocular adverse events (AEs), serious adverse events (SAEs), ocular assessments, deaths, laboratory test results, vital signs and antibodies to ranibizumab. Safety endpoints were analysed in the safety evaluable populations for the treatment groups, which grouped subjects according to the actual treatment received.

AEs for the final study data were mapped to terms defined by the Medical Dictionary for Regulatory Activities (MedDRA) and were tabulated by System Organ Class (SOC) and Preferred Term (PT).

Patient exposure

Overall exposure in the two pivotal studies is summarised in Table 10.

Table 10: Overall exposure in pivotal clinical studies BRAVO and CRUISE

Study	Duration	Sham/0.5 mg	0.3 mg	0.5 mg	Pooled (0.3+0.5)	Total
BRAVO	12 months	131	134	130	264	395
CRUISE	12 months	129	132	129	261	390
Total			266	259	552	

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In the *6 month treatment period***,** the pooled safety evaluable population included a total of 785 patients consisting of 260 treated with sham injections, 266 treated with ranibizumab 0.3 mg and 259 treated with ranibizumab 0.5 mg. Exposure during the 6 month treatment period in the pooled safety evaluable patients is summarised in Table 11.

Table 11: Exposure during the 6 month treatment period pooled pivotal studies: safety evaluable patients.

	Sham (n=260)	Ranibizumab 0.3 mg (n=266)	Ranibizumab 0.5 mg (n=259)
Injections – Total	1436	1534	1465
Injections - mean (SD)	5.5 (1.1)	5.8 (0.8)	5.7 (1.0)
1 injection	8 (3.1)	4 (1.5)	8 (3.1)
2 injections	5 (1.9)	2 (0.8)	1 (0.4)
3 injections	7 (2.7)	1 (0.4)	2 (0.8)
4 injections	6 (2.3)	3 (1.1)	3 (1.2)
5 injections	31 (11.9)	25 (9.4)	33 (12.7)
6 injections	203 (78.1)	231 (86.8)	212 (81.9)
Treatment duration days [a]			
Mean (SD) days	141.4 (34.0) [range: 1-171]	147.9 (22.4) [range: 1-176]	145.8 (28.5) [range: 1-74]

[a] = Number of days from the first injection to the last injection on or prior to the Month 5 visit.

In the *12 month study period*, the pooled safety evaluable population included a total of 525 patients treated with either ranibizumab 0.3 mg (n=266) or 0.5 mg (n=259). In the entire 12 month period, a total of 4660 ranibizumab injections were administered (2411 in the 0.3 mg group and 2249 in the 0.5 mg group). The mean number of ranibizumab

injections received from Day 0 to Month 12 per patient was 8.9 (9.1 and 8.7 injections in the 0.3 mg and 0.5 mg groups, respectively).

In the *6 month observation period*, 501 (95.4%) patients received an injection of ranibizumab (257 [96.6%] and 244 [94.2%] in the 0.3 mg and 0.5 mg groups, respectively). Of the 64 patients (12.8%) who received no ranibizumab injection, 24 had discontinued from the study during the treatment period and were not evaluated for the need for re-treatment in the observation period. Overall, the mean number of injections in the 6 month observation period was 3.3 (3.4 and 3.2 for the 0.3 and 0.5 mg groups, respectively). The majority of patients received their first injection during the 6 month observation period at either the Month 6 (48.5%) or Month 7 (26.3%) visit. Of the 260 patients who were randomly assigned to receive sham injection during the 6 month treatment period, 225 (86.5%) received a 0.5 mg injection during the 6 month observation period. In the 6 month observation period, sham/0.5 mg patients received a mean (SD) of 4.1 (1.7) injections in ***BRAVO*** and 4.4 (1.7) injections in ***CRUISE,*** with the possible number of injections being 6 in both studies.

Evaluator Comment

The baseline demographic characteristics of the safety evaluable population were consistent with those of the randomized patients in the three treatment groups. This is not surprising as the patient numbers were almost identical in the two populations. The number of patients in the randomized vs safety evaluable populations in the pooled data for the two pivotal studies was sham (264 vs 260), 0.3 mg (266 vs 266) and 0.5 mg (261 vs 259).

Adverse events

All adverse events (irrespective of relationship to treatment)

Overview

An overview of adverse events during the 6 month treatment period and the 12 month study period in the pooled safety evaluable patients is provided in Table 12. In the 6 month treatment period, ocular AEs were reported more frequently in patients in the ranibizumab 0.3 mg (80.8% [n=215]) and 0.5 mg (81.1% [n=210]) groups than in the sham group (76.9% [n=200]). However, non-ocular AEs were reported with similar frequencies in patients in the sham (51.5% [n=134]), 0.3 mg (52.6% [n=140]) and 0.5 mg (52.9% [n=137]) groups. In the three treatment groups, ocular AEs occurred about 26% to 28% more frequently than non-ocular AEs. In the 12 month study period, ocular AEs were reported in 90.2% (n=240) of patients in the ranibizumab 0.3 mg group and 88.4% (n=229) of patients in the ranibizumab 0.5 mg group, and non-ocular AEs were reported in 72.9% (n=194) in the 0.3 mg and 67.2% (n=174) in the 0.5 mg group. The AE data from the 6 month observational period in the sham/0.5 mg groups from the two pivotal studies were not pooled but presented separately.

Table 12: Overview of adverse events during the 6 month treatment and 12 month study period in BRAVO and CRUISE pooled safety evaluable patients

	6-month treatment			12-month study		
		Ranibizumab		Ranibizumab		
	Sham n=260	0.3 mg n=266	0.5 mg n=259	0.3 mg n=266	0.5 mg n=259	Pooled n=525
Adverse event category	n (%)					
Ocular events, study eye						
Any adverse event	200 (76.9)	215 (80.8)	210 (81.1)	240 (90.2)	229 (88.4)	469 (89.3)
Adverse event that led to treatment discontinuation	5 (1.9)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.8)	3 (0.6)
Serious adverse event	8 (3.1)	7 (2.6)	4 (1.5)	11 (4.1)	10 (3.9)	21 (4.0)
Key serious adverse events						
Cataract traumatic	0	0	0	0	0	0
Endophthalmitis	0	0	1 (0.4)	0	1 (0.4)	1 (0.2)
Intraocular inflammation	0	0	0	0	0	0
Intraocular pressure increased	0	0	0	0	0	0
Retinal artery occlusion	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Retinal detachment	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Retinal tear	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Retinal pigment epithelium detachment	0	0	0	0	0	0
Retinal pigment epithelium tear	0	0	0	0	0	0
Vitreous hemorrhage	1 (0.4)	0	0	0	0	0
Ocular events, fellow eye						
Any adverse event	60 (23.1)	63 (23.7)	73 (28.2)	95 (35.7)	103 (39.8)	198 (37.7)
Adverse event that led to treatment discontinuation	1 (0.4)	0	0	0	0	0
Serious adverse event	0	3 (1.1)	2 (0.8)	3 (1.1)	3 (1.2)	6 (1.1)
Non-ocular events						
Any adverse event	134 (51.5)	140 (52.6)	137 (52.9)	194 (72.9)	174 (67.2)	368 (70.1)
Adverse event that led to treatment discontinuation	2 (0.8)	2 (0.8)	3 (1.2)	2 (0.8)	4 (1.5)	6 (1.1)
Serious adverse event	15 (5.8)	23 (8.6)	23 (8.9)	35 (13.2)	34 (13.1)	69 (13.1)

Note: Table entries are number (%) of patients with at least 1 adverse event of the type specified.

Ocular adverse events

In the *6 month treatment period*, ocular AEs in the study eye were reported in 76.9% (n=200), 80.8% (n=215) and 81.1% (n=210) of patients in the sham, 0.3 mg and 0.5 mg groups, respectively (Table 13).

Table 13: Ocular AEs in the study eye during the 6 month treatment period (occurring in ≥ 5% of patients in any group) in BRAVO and CRUISE pooled safety evaluable patients

		Ranibizumab	
	Sham n=260	0.3 mg n=266	0.5 mg n=259
MedDRA preferred term		n (%)	
Any adverse event	200 (76.9)	215 (80.8)	210 (81.1)
Conjunctival hemorrhage	97 (37.3)	137 (51.5)	124 (47.9)
Retinal exudates	33 (12.7)	69 (25.9)	54 (20.8)
Eye pain	32 (12.3)	44 (16.5)	45 (17.4)
Retinal vascular disorder	24 (9.2)	30 (11.3)	32 (12.4)
Retinal hemorrhage	29 (11.2)	32 (12.0)	29 (11.2)
Maculopathy	19 (7.3)	36 (13.5)	28 (10.8)
Retinal depigmentation	11 (4.2)	17 (6.4)	23 (8.9)
Foreign body sensation in eyes	13 (5.0)	10 (3.8)	18 (6.9)
Myodesopsia	6 (2.3)	26 (9.8)	18 (6.9)
Eye irritation	16 (6.2)	14 (5.3)	17 (6.6)
Intraocular pressure increased	6 (2.3)	18 (6.8)	17 (6.6)
Ocular vascular disorder	13 (5.0)	17 (6.4)	17 (6.6)
Ocular hyperemia	7 (2.7)	18 (6.8)	13 (5.0)
Vitreous hemorrhage	15 (5.8)	11 (4.1)	9 (3.5)
Macular edema	16 (6.2)	9 (3.4)	5 (1.9)

Note: Table entries are number (%) of patients with at least 1 AE of the specified type.

In the *6 month treatment period*, the most frequently reported ocular AE in the study eye in the three groups was conjunctival haemorrhage and this AE was reported in about 11% to 14% more patients in the ranibizumab groups than in the sham group. Other AEs in the study eye reported more frequently in both ranibizumab dose groups than in the sham group were retinal exudates, eye pain, retinal vascular disorder, maculopathy, retinal depigmentation, myodesopia, increased intraocular pressure, ocular vascular disorder and ocular hyperaemia. Ocular AEs in the study eye reported more frequently in the sham group than in at least one of the ranibizumab dose groups were foreign body sensation in the eye, eye irritation, vitreous haemorrhage and macular oedema. Overall, there was no consistent association between ocular AEs in the study eye and ranibizumab dose.

In the *6 month treatment period*, ocular AEs in the study eye classified by investigators as severe were experienced by 3.8% (n=10), 3.4% (n=9) and 1.9% (n=5) of patients in the sham, 0.3 mg and 0.5 mg groups, respectively. The most commonly reported ocular severe AE in the study eye was macular oedema in the sham group (1.5% [n=4]), compared with 0.4% [n=1] and 0% in the 0.3 mg and 0.5 mg groups, respectively. Each of the other severe AEs occurred in ≤ 2 patients (≤ 0.8%) in each treatment group. The only severe AE reported in both ranibizumab dose groups was conjunctival haemorrhage (0.4% [n=1] in both groups vs 0.8% [n=2] in the sham group). There were three ocular severe AEs reported in the sham group but in neither ranibizumab dose group: macular ischaemia (0.4% [n=1]); retinal vein occlusion (0.4% [n=1]); and vitreous haemorrhage (0.4% [n=1]).

In the *12 month study period*, ocular AEs in the study eye were reported in 90.2% (n=240) of patients in the 0.3 mg group and 88.4% (n=229) of patients in the 0.5 mg group. The most frequently reported ocular AEs (≥ 20%) in the combined ranibizumab group were

conjunctival haemorrhage (52.2%), retinal exudates (29.0%), retinal haemorrhage (25.0%), maculopathy (21.3%) and retinal vascular disorder (20.6%).

In the *12 month study period,* ocular AEs in the study eye classified by investigators as severe were experienced by 3.4% (n=9) patients in the 0.3 mg group and 3.9% (n=10) patients in the 0.5 mg group. The most commonly reported ocular AEs categorised as severe in the pooled ranibizumab dose groups (≥ 2 patients) were conjunctival haemorrhage (3 patients, 1 in the 0.5 mg group and 2 in the 0.3 mg group), increased intraocular pressure (3 patients, all in the 0.5 mg group) and macular oedema (2 patients, 1 in each group). There was no notable dose response relationship between ranibizumab and ocular severe AEs.

In the *6 month observation period*, ocular AEs occurring with an incidence of ≥ 5% in the sham/0.5 mg group in either ***BRAVO*** (n=115) or ***CRUISE*** (n=110) were (respectively): any AE (65.2% [n=75] vs 77.3% [n=85]); conjunctival haemorrhage (37.4% [n=43] vs 29.1% [n=32]): maculopathy (14.8% [n=17] vs 23.6% [n=26]); retinal haemorrhage (11.3% [n=13] vs 10.0% [n=11]); retinal vascular disorder (10.4% [n=12] vs 12.7% [n=14]); retinal depigmentation (8.7% [n=10] vs 9.1% [n=10]); myodesopsia (4.3% [n=5] vs 7.3% [n=8]); eye pain (7.0% [n=8] vs 7.3% [n=8]); retinal exudates (7.0% [n=8] vs 10.0% [n=11]); optic disc vascular disorder (0% vs 5.5% [n=6]); and vitreous detachment (1.7% [n=2] vs 5.5% [n=6]).

Evaluator Comment

The 6 month treatment period data showed that most ocular AEs in the study eye occurred more commonly in the ranibizumab groups compared with the sham group. This is not unexpected as ranibizumab was administered by IVT injection compared with non-penetrative sham treatment. The most frequently reported ocular AEs in the study eye occurring with an incidence of ≥ 10% in at least one of the ranibizumab dose groups, and more commonly in both groups than in the sham group, were conjunctival haemorrhage, retinal exudates, eye pain and retinal vascular disorder. Most ocular AEs in the study eye occurring in ≥ 5% of patients in any of the three treatment groups occurred more frequently in both ranibizumab dose groups than in the sham group. Ocular severe AEs in the 6 month treatment period were reported more frequently in the sham group than in both ranibizumab dose groups. In the 12 month study period, most patients (~89%) in both ranibizumab dose groups experienced an ocular AE in the study eye with the most frequent being conjunctival haemorrhage (~52%). Ocular severe AEs in the 12 month study period occurred in 3.4% of patients in the 0.3 mg group and 3.9% of patients in the 0.5 mg group. Overall, the 6 month treatment period and 12 month study data did not demonstrate a consistent dose response relationship between ocular AEs and ranibizumab 0.3 mg and 0.5 mg. Overall, the ocular AEs reported in the study eye in patients with RVO are consistent with those previously reported for ranibizumab in patients with wet AMD and included in the currently approved Lucentis PI.

Non-ocular adverse events

In the *6 month treatment period*, non-ocular AEs were reported in 51.5% (n=134), 52.6% (n=140) and 52.9% (n=137) of patients in the sham, 0.3 mg and 0.5 mg groups, respectively (Table 14). The most frequently reported non-ocular AE was hypertension which was reported in 8.1% (n=21), 6.0% (n=16) and 5.0% (n=13) of patients in the sham, 0.3 mg and 0.5 mg groups, respectively. The only other non-ocular AE reported with an incidence of ≥ 5% in both ranibizumab dose groups was nasopharyngitis.

Table 14: Non-ocular AEs during the 6 month treatment period (occurring in ≥ 2% of patients in any group) in BRAVO and CRUISE pooled safety evaluable patients

		Ranibizumab	
	Sham n=260	0.3 mg n=266	0.5 mg n=259
MedDRA preferred term		n (%)	
Any adverse event	134 (51.5)	140 (52.6)	137 (52.9)
Nasopharyngitis	10 (3.8)	14 (5.3)	14 (5.4)
Hypertension	21 (8.1)	16 (6.0)	13 (5.0)
Influenza	5 (1.9)	4 (1.5)	8 (3.1)
Sinusitis	5 (1.9)	14 (5.3)	8 (3.1)
Back pain	2 (0.8)	4 (1.5)	7 (2.7)
Headache	9 (3.5)	13 (4.9)	7 (2.7)
Arthralgia	2 (0.8)	3 (1.1)	6 (2.3)
Upper respiratory tract infection	4 (1.5)	7 (2.6)	6 (2.3)
Fall	6 (2.3)	2 (0.8)	5 (1.9)
Dizziness	9 (3.5)	6 (2.3)	2 (0.8)
Diarrhea	7 (2.7)	5 (1.9)	1 (0.4)
Vertigo	7 (2.7)	3 (1.1)	1 (0.4)

Note: Table entries are number (%) of patients with at least 1 AE of the specified type.

In the *6 month treatment period*, non-ocular AEs classified by investigators as severe were reported in 5.0% of patients in the sham group, 5.6% of patients in the 0.3 mg group and 7.7% of patients in the 0.5 mg group. Each of the severe AEs occurred in ≤ 2 (≤ 0.8%) patients in each treatment group. The only AEs classified as severe and occurring in both ranibizumab dose groups and not in the sham treatment group were cellulitis (0.4% [n=1] in both ranibizumab groups) and MI (0.4% [n=1] in both ranibizumab groups). There were no other notable imbalances between the three treatment groups.

In the *12 month study period*, non-ocular AEs were reported in 72.9% (n=194) and 67.2% (n=174) patients in the ranibizumab 0.3 mg and 0.5 mg groups, respectively. Non-ocular AEs reported in ≥ 5% of patients in at least one of the ranibizumab dose groups (0.3 mg vs 0.5 mg) were: hypertension 10.5% (n=28) vs 9.3% (n=24); nasopharyngitis 7.5% (n=20) vs 7.7% (n=20); sinusitis 7.5% (n=20) vs 5.8% (n=15); influenza 3.0% (n=8) vs 5.4% (n=14); and upper respiratory tract infection 3.0% (n=8) vs 5.0% (n=13).

In the *12 month study period*, non-ocular AEs classified as severe by investigators were experienced by 24 patients (9.0%) in the 0.3 mg group and 33 patients (12.7%) in the 0.5 mg group. With the exception of hypertension (experienced by 4 patients overall), cardiac failure congestive and pneumonia (3 patients each), and cellulitis, coronary artery disease, gastroenteritis viral, arthritis, and MI (2 patients each), all other AEs classified as severe were experienced by only 1 patient overall during the study.

In the *6 month observation period*, in the sham/0.5 mg group non-ocular adverse events were reported in 49.6% (57/115) of patients in ***BRAVO*** and 50.0% (55/110) of patients in ***CRUISE***. The most common non-ocular AE in both studies was hypertension (5.2% [n=6] ***BRAVO*** and 5.5% [n=6] ***CRUISE***). The only other non-ocular AE occurring in ≥ 5% of patients was nasopharyngitis (5.5% [n=6] in CRUISE).

Evaluator Comment

In the 6 month treatment period, non-ocular AEs (any) occurred with similar frequencies in the sham, 0.3 mg and 0.5 mg treatment groups. The non-ocular AE pattern was

generally similar for the three treatment groups and there was no notable association between AE frequency and ranibizumab dose. In the 12 month study period, the cumulative incidence of non-ocular AEs in both the 0.3 mg and 0.5 mg treatment groups was higher than that during the 6 month treatment period. The increased incidence most likely reflects greater exposure to ranibizumab. The non-ocular AE profile for the combined ranibizumab group at 12 months was similar to that at 6 months, with the three most common AEs being hypertension (9.9%), nasopharyngitis (7.6%) and sinusitis (6.7%). There was no notable association between AEs and ranibizumab dose in the 12 month data. Overall, the 6 month treatment and 12 month study period data do not give rise to new or unexpected concerns relating to the non-ocular safety of ranibizumab.

Safety concerns identified in the Risk Management Plan (RMP) for ranibizumab

The submission included an investigation of important identified and potential risks (ocular and systemic) associated with ranibizumab treatment and reported in the RMP from clinical studies in patients with wet-AMD and diabetic macular oedema (DME), and from postmarketing reports.

Ocular AEs (any) in the study eye in the 6 month treatment period reflecting the RMP safety concerns occurred with similar frequencies in patients in the sham, 0.3 mg and 0.5 mg groups (31.2% [n=81], 32.0% [n=85] and 30.5% [n=79], respectively) (Table 15). In the 12 month study period, ocular AEs (any) reflecting the RMP safety concerns occurred in 53.4% (n=142) of patients in the 0.3 mg group and 50.2% (n=130) in the 0.5 mg group. The most common ocular AE in the study eye reflecting the RMP safety concerns in the 12 month study period in the combined ranibizumab group was deterioration of retinal blood flow (25.5% [n=134]), followed by intraocular inflammation (20.2% [n=106]), intraocular pressure increased (12.0% [n=63]), traumatic cataract (5.5% [n=29]), vitreous haemorrhage (4.4% [n=23]), retinal tear (0.6% [n=3]), endophthalmitis (0.2% [n=1]) and retinal detachment (0.2% [n=1]). Retinal pigment epithelial tear was reported in no patients. The term "intraocular inflammation" appeared to include a number of individual preferred terms (that is, anterior chamber inflammation, hypopyon, iridocyclitis, iritis, uveitis, viral iritis and vitritis).

Table 15: Ocular AEs in the study eye reflecting RMP safety concerns in the 6 month treatment period: pooled safety evaluable patients

Ocular Safety Concern	Sham (n=260)	Ranib 0.3 mg (n=266)	Ranib 0.5 mg (n=259)
Any AE	31.2% (n=81)	32.0% (n=85)	30.5% (n=79)
Deterioration of retinal blood flow	14.6% (n=38)	13.2% (n=35)	13.5% (n=35)
Intraocular inflammation	11.5% (n=30)	10.9% (n=29)	7.3% (n=19)
Intraocular pressure increased	3.8% (n=10)	7.1% (n=19)	6.9% (n=18)
Vitreous haemorrhage	5.8% (n=15)	4.1% (n=11)	3.5% (n=9)
Traumatic cataract	2.3% (n=6)	1.5% (n=4)	2.3% (n=6)
Retinal tear	0%	0.4% (n=1)	0.8% (n=2)
Retinal detachment	0.4% (n=1)	0.4% (n=1)	0%
Endophthalmitis	0%	0%	0.4% (n=1)
Retinal pigment epithelial tear	0%	0%	0%

Note: Multiple occurrences of the same event in a patient were only counted once.

Systemic AEs in the 6 month treatment period reflecting the RMP safety concerns occurred more commonly in the sham group (20.8% [n=54]) than in both the ranibizumab 0.3 mg

group (18.4% [n=49]) and the ranibizumab 0.5 mg group (15.8% [n=41]) (Table 16). In the 12 month study period, systemic AEs reflecting the RMP safety concerns occurred in 27.1% (n=72) of patients in the 0.3 mg group and 23.6% (n=61) of patients in the 0.5 mg group. The most common systemic AE reflecting the RMP safety concerns in the 12 month study period (0.3 mg vs 0.5 mg) was hypertension (12.0% [n=32] vs 12.0% [n=31], followed by hypersensitivity (11.7% [n=31] vs 9.3% [n=24]), other arterial thromboembolic events (2.3% [n=6] vs 1.9% [n=5]), non-ocular haemorrhage (2.3% [n=6] vs 1.2% [n=3]), MI (0.4% [n=1] vs 1.2% [n=3]), proteinuria (0% vs 0.4% [n=1]) and venous thromboembolic events (0.4% [n=1] vs 0%).

Table 16: Systemic AEs reflecting the RMP systemic safety concerns in the 6 month treatment period: pooled safety evaluable patients

Systemic Safety Concern	Sham (n=260)	Ranib 0.3 mg (n=266)	Ranib 0.5 mg (n=259)
Any AE	20.8% (n=54)	18.4% (n=49)	15.8% (n=41)
Hypersensitivity	8.1% (n=21)	9.4% (n=25)	6.9% (n=18)
Hypertension	10.0% (n=26)	6.8% (n=18)	6.6% (n=17)
Non-ocular haemorrhage	2.3% (n=6)	1.9% (n=5)	0.8% (n=2)
Proteinuria	0%	0%	0%
Myocardial infarction	0.4% (n=1)	0.4% (n=1)	0.8% (n=2)
Other arterial thromboembolic events	0.8% (n=2)	1.1% (n=3)	1.5% (n=4)
Venous thromboembolic events	0.4% (n=1)	0.4% (n=1)	0%

Note: Multiple occurrences of the same event in a patient were only counted once. Includes ocular and non-ocular adverse events.

Evaluator Comment

In the 6 month treatment period, individual ocular AEs reflecting RMP safety concerns and occurring with a greater incidence in the pooled ranibizumab group than in the sham group were intraocular inflammation (9.1% [n=48] vs 11.5% [n=30]), increased intraocular pressure (7.0% [n=37] vs 3.8% [n=10]), retinal tear (0.6% [n=3] vs 0%) and endophthalmitis (0.2% [n=1] vs 0%). In neither the 6 month treatment period nor the 12 month study period did the incidence of either systemic or ocular AEs notably differ between the 0.3 mg and 0.5 mg ranibizumab groups. Perusal of the RMP suggests that the term "hypersensitivity" included hypersensitivity reactions (SMQ narrow terms of anaphylactic, angioedema, severe cutaneous reactions), and the numerous listed preferred terms included ocular AEs such as allergic scleritis, allergic keratitis, and eye allergy.[12] No categorization of the individual AEs contributing to the term "hypersensitivity" could be readily identified in the submission.

The results indicated that hypertension and hypersensitivity were the two most commonly occurring AEs reflecting RMP systemic safety concerns during both the 6 month treatment period and the 12 month study period. However, the 6 month treatment period data showed that there was no increased risk of these two events in ranibizumab treated patients compared with sham treated patients. In the 6 month treatment period, there was a small increased risk of MI and other thromboembolic arterial events in the

[12] Standardised MedDRA Queries (SMQs) are groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification.

combined ranibizumab compared with the sham group but the number of events were small and the differences of doubtful clinical significance.

Treatment related adverse events

Ocular adverse events - treatment related

In the *6 month treatment period*, treatment related ocular AEs were reported in 27.3% (n=71), 38.3% (n=102) and 32.4% (n=259) of patients in the sham, ranibizumab 0.3 mg and ranibizumab 0.5 mg groups, respectively. The most frequently reported treatment related ocular AEs were conjunctival haemorrhage (19.2% [n=50], 26.3% [n=70] and 22.0% [n=57] of patients in the sham, 0.3 mg and 0.5 mg groups, respectively), and eye pain (7.3% [n=19], 10.9% [n=29] and 13.5% [n=35], respectively). All other treatment related ocular AEs occurred in ≤ 6.0% of patients in one or other of the ranibizumab dose groups. In addition to conjunctival haemorrhage and eye pain, other treatment related ocular AEs reported in ≥ 2% of patients in both ranibizumab dose groups and more frequently than in the sham group (0.3 mg vs 0.5 mg vs sham, respectively) were: eye irritation (3.4% [n=9] vs 3.4% [n=9] vs 1.9%, [n=5]); intraocular pressure increased (4.9% [n=13] vs 3.5% [n=9] vs 1.5% [n=4]); myodesopsia (6.0% [n=16] vs 2.3% [n=6] vs 0%); and ocular hyperaemia (2.6% [n=7] vs 2.3% [n=6] vs 0.8% [n=2]).

In the *12 month study period*, treatment related ocular AEs were reported in 40% (210/525) of patients in the combined ranibizumab group. The three most commonly reported treatment related ocular AEs in the combined ranibizumab group were conjunctival haemorrhage (26.9%), eye pain (13.1%) and increased intraocular pressure (6.3%). All other events were reported in < 5% of patients in the combined ranibizumab group. There was no notable dose relationship between treatment related ocular AEs and ranibizumab 0.3 mg and 0.5 mg.

Evaluator Comment

The treatment related ocular AEs reported with ranibizumab are consistent with those known to be associated with the drug. The treatment related ocular AE profile was similar to the ocular AE profile irrespective of treatment. The incidence of treatment related ocular AEs was similar in the ranibizumab 0.3 mg and 0.5 mg groups, and no notable dose response relationship was observed. The results do not give rise to new safety signals associated with ranibizumab.

Non-ocular adverse events - treatment related

In the *6 month treatment period*, treatment related non-ocular AEs were reported in 1.5% of all patients (8/525).The only treatment related non-ocular AE occurring in ≥ 2 patients in at least one of the treatment groups was headache (2 patients in the sham group). Treatment related AEs occurring in 1 patient in the combined ranibizumab group, but not in the sham group, were myocardial infarction, sinusitis, cerebral haemorrhage, dizziness, pre-syncope, anxiety and hypertension. Treatment related AEs occurring in the sham group, but not in the combined ranibizumab group, were headache (n=2) and thalamus haemorrhage (n=1).

In the *12 month study period*, treatment related non-ocular AEs occurred in 1.5% (n=8) of patients in the combine ranibizumab group (1.5% [n=4] in both the 0.3 and 0.5 mg groups). Each of the 12 treatment related non-ocular AEs in the combined ranibizumab group in the 12 month study period was reported in 1 patient only.

Evaluator Comment

Treatment related non-ocular AEs were reported infrequently in all treatment groups in both the 6 month treatment period and the 12 month study period. The results do not give rise to new safety signals associated with ranibizumab.

Deaths and other serious adverse events

Deaths

A total of 7 patients died in studies involving patients with RVO: 5 during the two pivotal studies and 2 in the extension study ***FVF3426g***.

In ***BRAVO***, 3 deaths occurred in the 12 month study period: *1 in an 80 year old male* (with a history of myocardial infarction, diabetes mellitus, pulmonary fibrosis, aortic stenosis) due to respiratory failure on Day 287, and considered by the investigator to be unrelated to treatment (sham/0.5 mg group; 6 sham treatments and 3 treatments with 0.5 mg); *1 in a 79 year old male* (with a history of hypertension) due to pneumonia on Day 314 considered by the investigator to be unrelated to treatment (0.3 mg group; 11 days after ninth treatment with 0.3 mg); and *1 in a 78 year old male* (with a history of haemorrhagic stroke about 1.5 years before study entry) due to respiratory failure on Day 177, preceded by a cerebral haemorrhage on Day 169 and respiratory failure on Day 174, and considered by the investigator to be related to the study drug. This patient received his last dose of ranibizumab 0.5 mg 18 days before the onset of the cerebral haemorrhage (on Day 151).

In ***CRUISE***, 2 deaths occurred during the 12 month study period: *1 in an 83 year old female* due to gastric cancer on Day 225 and considered by the investigator to be unrelated to treatment (sham/0.5 mg group; 101 days after fifth sham treatment with no 0.5 mg treatments being given); and *1 in an 85 year old male* (with a history of hypertension and heart surgery for aortic aneurysm) of unknown cause on Day 223 and considered by the investigator to be unrelated to the study drug (0.5 mg group; 13 days after eighth treatment)

In ***FVF3426g,*** there were 2 deaths: *1 in an 84 year old male* due to congestive cardiac failure about 9 months after last 0.5 mg dose [previously enrolled in BRAVO; unspecified number of injections prior to the event]; *1 in a 60 year old male* (with a history of congestive cardiac failure, Ebstein's anomaly, hypertension, atrial fibrillation, atrial flutter, cardiac ablation and gout) in the sham/0.5 mg group (previously enrolled in BRAVO) due to sepsis secondary to cardiac failure and sepsis about 6 weeks after 0.5 mg.

Evaluator Comment

It was considered that a causal association between the study drug and death is unlikely in 5 of reported cases, but cannot be excluded in 1 case in BRAVO considered by the investigator to be related to the study drug and 1 case in CRUISE with an unknown cause.

Ocular serious adverse events (SAEs)

In the *6 month treatment period*, ocular SAEs were reported in 3.1% (n=8), 2.6% (n=7) and 1.5% (n=4) of patients in the sham, 0.3 mg and 0.5 mg groups, respectively. The only SAE occurring in ≥ 1% of patients in any of the three treatment groups was macular oedema (1.2% [n=3] in the sham group vs 0.4% [n=2] in the combined ranibizumab group). In the combined ranibizumab group, macular oedema was the only ocular SAE that occurred in more than 1 patient. SAEs occurring in 1 patient in the combined ranibizumab group and no patients in the sham group were: corneal abrasion; corneal oedema; endophthalmitis; iris neovascularization; retinal artery occlusion; retinal detachment; retinal ischaemia; retinal tear; retinal vascular disorder; and retinal vascular occlusion. There was no pattern of increased SAEs in the 0.5 mg compared with the 0.3 mg group.

In the *12 month study period*, ocular SAEs were reported in 4.0% (n=21) of patients in the combined ranibizumab group. There were a total of 16 different ocular SAEs reported in the combined ranibizumab group during the 12 month period. The only ocular SAEs occurring in more than 1 patient in this group were macular oedema (n=7 [1.3%]), and retinal vein occlusion (n=4 [0.8%]). There was no pattern of increased SAEs in the 0.5 mg group compared with the 0.3 mg group

Non-ocular serious adverse events (SAEs)

In the *6 month treatment period*, non-ocular SAEs were reported in 5.8% (n=15), 8.6% (n=23) and 8.9% (n=23) of patients in the sham, 0.3 mg and 0.5 mg groups, respectively. SAEs occurring more commonly in the combined ranibizumab group than in the sham group were: cellulitis (0.4% [n=2] vs 0%); colitis (0.4% [n=2] vs 0%); MI (0.4% [n=2] vs 0%); small intestinal obstruction (0.4% [n=2] vs 0%); and syncope (0.4% [n=2]). SAEs occurring more commonly in the sham group than in the combined ranibizumab group were: coronary artery disease (0.8% [n=2] vs 0.4% [n=2]); and gastric cancer (0.4% [n=1] vs 0.2% [n=1]).

In the *12 month study period*, 13.1% (n=69) of patients in the combined ranibizumab group experienced a SAE. The most common of these was pneumonia (1.0% [n=5]). The only two other SAEs occurring in more than 2 patients in the combined ranibizumab group were congestive cardiac failure (n=4 [0.8%]) and hypertension (n=4 [0.8%]). There were no notable differences in the incidence of SAEs between the 0.3 mg and 0.5 mg groups.

SAEs reflecting the safety concerns identified in the RMP

Ocular SAEs (any) in the 6 month treatment period reflecting the RMP safety concerns occurred more commonly in patients in the sham group (3.1% [n=8]) compared with patients in both the 0.3 mg group (1.9% [n=5]) and the 0.5 mg group (1.2% [n=3]) (Table 17). In the 12 month study period, ocular SAEs reflecting the RMP safety concerns occurred in 3.2% (n=17) of patients in the combined ranibizumab group (3.4% [n=9] and 3.1% [n=8] in the 0.3 mg and 0.5 mg group, respectively). The most commonly occurring ocular SAE reflecting the RMP safety concerns in patients in this group was deterioration of retinal blood flow (1.5% [n=8]), followed by intraocular inflammation (1.3% [n=7]).

Table 17: Ocular SAEs reflecting the RMP ocular safety concerns in the 6 month treatment period: safety evaluable patients

Ocular Safety Concern	Sham (n=260)	Ranib 0.3 mg (n=266)	Ranib 0.5 mg (n=259)
Any SAE	3.1% (n=8)	1.9% (n=5)	1.2% (n=3)
Deterioration of retinal blood flow	1.5% (n=4)	0.8% (n=2)	0.8% (n=2)
Intraocular inflammation	1.2% (n=3)	0.8% (n=2)	0%
Intraocular pressure increased	0%	0%	0%
Vitreous haemorrhage	0.4% (n=1)	0%	0%
Traumatic cataract	0%	0%	0%
Retinal tear	0%	0.4% (n=1)	0%
Retinal detachment	0%	0.4% (n=1)	0%
Endophthalmitis	0%	0%	0.4% (n=1)
Retinal pigment epithelial tear	0%	0%	0%

Note: Multiple occurrences of the same event in a patient were only counted once.

Systemic SAEs (any) in the 6 month treatment period reflecting the RMP safety concerns occurred more commonly in patients in the sham group (1.5% [n=4]) compared with patients in both the 0.3 mg (2.6% [n=7]) and 0.5 mg (1.9% [n=5]) groups (Table 18).

Table 18: Systemic SAEs reflecting the RMP systemic safety concerns in the 6 month treatment period: safety evaluable patients

Systemic Safety Concern	Sham (n=260)	Ranib 0.3 mg (n=266)	Ranib 0.5 mg (n=259)
Any SAE	1.5% (n=4)	2.6% (n=7)	1.9% (n=5)
Hypersensitivity	0%	0.4% (n=1)	0%
Hypertension	0.4% (n=1)	0.8% (n=2)	0%
Non-ocular haemorrhage	0.4% (n=1)	0.8% (n=2)	0.8% (n=2)
Proteinuria	0%	0%	0%
Myocardial infarction	0.4% (n=1)	0.4% (n=1)	0.8% (n=2)
Other arterial thromboembolic events	0.4% (n=1)	0%	0.8% (n=2)
Venous thromboembolic events	0.4% (n=1)	0.4% (n=1)	0%

Note: Multiple occurrences of the same event in a patient were only counted once. Includes ocular and non-ocular adverse events.

In the 12 month treatment period, systemic SAEs (any) reflecting RMP safety concerns occurred in 3.4% (n=18) of patients in the combined ranibizumab group (3.8% [n=10] and 3.1% [n=8] in the 0.3 mg and 0.5 mg groups, respectively). The most commonly occurring systemic SAE reflecting the RMP safety concerns in patients in the combined ranibizumab group was other arterial thromboembolic events (1.0% [n=5]). Other systemic SAEs reflecting the RMP safety concerns in the 12 month treatment period and occurring in more than 1 patient in the combined ranibizumab group were hypertension, non-ocular haemorrhage and myocardial infarction, with each event occurring in 4 (0.8%) patients.

Evaluator Comment

In the 6 month treatment period, total ocular SAEs reflecting the RMP safety concerns occurred more commonly in the sham group than in both the ranibizumab dose groups. Individual ocular SAEs occurring more commonly in the combined ranibizumab group than in the sham group were endophthalmitis (0.2% [n=1] vs 0), retinal tear (0.2% [n=1] vs 0) and retinal detachment (0.2% [n=1] vs 0). The number of patients with ocular SAEs reflecting the RMP safety concerns was small for all events (< 5 patients) in the sham group and the combined ranibizumab group. In the 6 month treatment period, total systemic SAEs reflecting the RMP safety concerns occurred more commonly in both ranibizumab dose groups than in the sham group. Individual systemic SAEs occurring more commonly in the combined ranibizumab group than in the sham group were non-ocular haemorrhage (0.8% [n=4] vs 0.4% [n=1]), myocardial infarction (0.6% [n=3] vs 0.4% [n=1] and hypersensitivity (0.2% [n=1] vs 0%). The number of patients with systemic SAEs reflecting the RMP safety concerns was small for all events (< 5 patients) in the sham group and the combined ranibizumab group. In neither the 6 month treatment period nor the 12 month study period did the incidence of ocular or systemic SAEs reflecting the RMP safety concerns notably differ between the 0.3 mg and 0.5 mg doses.

Discontinuation due to adverse events

Discontinuation due to ocular adverse events

In the *6 month treatment period*, discontinuations due to ocular AEs in the study eye were reported in 1.9% (n=5) of patients in the sham group, 0.4% (n=1) in the 0.3 mg group and 0.4% (n=1) in the 0.5 mg group. The only ocular AEs resulting in discontinuation in patients in the ranibizumab groups were corneal oedema (0.4% [n=1] in the 0.3 mg and 0% in the 0.5 mg groups compared with 0% in the sham group), and endophthalmitis (0.4% [n=1] in the 0.5 mg and 0% in the 0.3 mg groups compared with 0% in the sham group). In the sham group, the following AEs resulted in discontinuation in 5 patients: macular oedema (0.8% [n=2]; retinal vein occlusion (0.8% [n=2]; iris neovascularization (0.4% [n=1]); and macular ischaemia (0.4% [n=1]).

In the *12 month study period*, ocular AEs in the study eye resulting in discontinuation occurred in 1 (0.4%) patient in the 0.3 mg group (corneal oedema), and 2 patients (0.8%) in the 0.5 mg group (1 x endophthalmitis, 1 x glaucoma, 1 x iris neovascularization).

Evaluator Comment

Discontinuations resulting from AEs were uncommon both in the 6 month treatment period in the sham and ranibizumab groups, and in the 12 month study period in the ranibizumab groups.

Discontinuation due to non-ocular adverse events

In the *6 month treatment period,* discontinuations due to non-ocular AEs were reported in 0.8% (n=2) of patients in the sham group, 0.8% (n=2) of patient in the 0.3 mg group and 1.2% (n=3) in the 0.5 mg group. None of the non-ocular AEs resulting in discontinuation occurred in more than 1 (0.4%) patient. Non-ocular AEs resulting in discontinuation (sham vs 0.3 mg vs 0.5 mg) were: coronary arteriosclerosis (0% vs 0% vs 0.4%); cerebral haemorrhage (0% vs 0% vs 0.4%); Alzheimer's dementia (0% vs 0.4% vs 0%); gastric cancer (0.4% vs 0% vs 0%); ocular herpes zoster (0% vs 0% vs 0.4%); hip fracture (0.4% vs 0% vs 0%); and MI (0% vs 0.4% vs 0%).

In the *12 month study period*, discontinuations due to non-ocular AEs occurred in 0.8% (n=2) of patients in the 0.3 mg group and 1.5% (n=4) of patients in the 0.5 mg group. The 2 non-ocular AEs resulting in discontinuation in the 2 patients in 0.3 mg group were rectal cancer and MI and in the 4 patients in the 0.5 mg group the 7 SAEs resulting in discontinuation were coronary arteriosclerosis, cerebral haemorrhage, CVA, respiratory failure, rectal cancer, ocular herpes zoster and myocardial infarction.

Evaluator Comment

Non-ocular AEs resulting in discontinuing in the 6 month treatment period were uncommon and occurred in 0.8% (n=2) of patients in the sham group and 1.0% (n=5) of patients in the pooled ranibizumab group (0.3 mg plus 0.5 mg).

Laboratory tests

Overview

Both studies included assessment of haematology, clinical chemistry, coagulation and urinalysis performed at screening and at the final Month 12 visit (or earlier in the case of discontinuation). In addition, the number and percentage of patients with positive serum antibodies to ranibizumab at baseline and during the study were also assessed.

Haematology

In ***BRAVO,*** in the 12 month study period laboratory haematology parameters above the upper limit of normal (ULN) in > 3% of patients in either ranibizumab group (0.3 mg vs 0.5 mg) were: lymphocytes (1.8% [2/114] vs 3.3% [4/123]); monocytes (3.5% [4/113] vs 1.6% [2/123]); and segmented neutrophils (5.6% [6/108] vs 2.5% [3/121]). In the 12 month study period laboratory haematology parameters below the lower limit of normal (LLN) in > 3% of patients in either ranibizumab group (0.3 mg vs 0.5 mg) were: haematocrit (6.4% [7/110] vs 2.6% [3/114]); haemoglobin (6.5% [7/107] vs 4.5% [5/112]); lymphocytes (4.5% [5/112] vs 1.7% [2/121]); and red blood cell count (3.7% [4/109] vs 2.6% [3/114]).

In ***CRUISE***, in the 12 month study period laboratory haematology parameters above the ULN in ≥ 3% of patients in either ranibizumab group (0.3 mg vs 0.5 mg) were: monocytes (4.2% [5/120] vs 2.9% [3/105]); segmented neutrophils (5.1% [6/118] vs 5.2% [6/118]); and white blood cell count (2.6% [3/115] vs 6.1% [6/99). In the 12 month study period, laboratory haematology parameters below the LLN in ≥ 3% of patients (0.3 mg vs 0.5 mg) were: haematocrit (4.5% [5/110] vs 2.9% [3/104]; haemoglobin 7.1% [8/112] vs 5.0% [5/101]; lymphocytes 1.7% [2/116] vs 3.0% [3/99]); and red blood cell count (6.4% [7/110] vs 3.8% [4/104]).

Evaluator Comment

In both pivotal studies, haematology abnormalities above or below normal limits in ≥ 3% patients with normal baseline levels were uncommon in the 12 month study period. There was consistency between the two studies with monocytes and segmented neutrophils above the ULN in ≥ 3% of patients occurring in at least one of the ranibizumab groups in both studies, and haematocrit, haemoglobin, lymphocytes and red blood cell count below the LLN in ≥ 3% of patients occurring in at least one of the ranibizumab groups in both studies. None of the haematology parameters in either of the studies was above the ULN in > 7% of patients or below the LLN in > 8% of patients. Anaemia was the most commonly reported haematology AE in the 12 month study period and was reported in 1.8% (10/525) of patients in the combined ranibizumab group. Anaemia is also identified as a commonly occurring AE in the approved PI.

Coagulation

In ***BRAVO***, in patients without an elevation at baseline, *prothrombin time* increased above the ULN in 9.9% (10/101) in the 0.3 mg group and 8.5% (9/106) in the 0.5 mg during the 12 month study period. In patients without a decrease at baseline, *prothrombin time* decreased to below the LLN in 1.9% (2/104) in the 0.3 mg group and 1.9% (2/104) in the 0.5mg group. In patients without an elevation at baseline, *activated partial prothrombin time* increased above the ULN in 1.0% (1/100) in the 0.3 mg group and 3.7% (4/109) in the 0.5 mg group. Of patients without a decrease at baseline, *activated prothrombin time* decreased to below the LLN in 14.9% (13/87) in the 0.3 mg group and in 6.9% (6/87) in the 0.5 mg group during the 12 month study period.

In ***CRUISE***, in patients without an elevation at baseline, *prothrombin time* increased above the ULN in 7.8% (8/102) in the 0.3 mg group and 14.4% (13/90) in the 0.5 mg group during the 12 month study period. In patients without a decrease at baseline, *prothrombin time* decreased to below the LLN in 0% (0/107) in the 0.3 mg group and 4.0% (4/100) of patients during the 12 month study period. In patients without an increase at baseline, *activated prothrombin time* increased to above the ULN in 3.0% (3/99) in the 0.3 mg group and in 12.6% (12/95) in the 0.5 mg group during the 12 month study period. In patients without a decrease at baseline, *activated prothrombin time* decreased to below the LLN in

9.5% (8/84) in the 0.3 mg group and in 8.1% (7/86) in the 0.5 mg group during the 12 month study period.

Evaluator Comment

In BRAVO, a greater proportion of patients with elevated baseline prothrombin times had elevations above the ULN during the 12 month study period compared with the proportion of patients with reduced baseline prothrombin with reductions below the LLN during the 12 month study period. Conversely, a lower proportion of patients with elevated baseline activated partial prothrombin times had elevations above the ULN during the 12 month study period compared with the proportion of patients with reduced baseline prothrombin with reductions below the LLN during the 12 month study period.

In CRUISE, a greater proportion of patients with elevated baseline prothrombin times had elevations above the ULN during the 12 month study period compared with the proportion of patients with reduced baseline prothrombin with reductions below the LLN during the 12 month study period. However, the proportion of patients with elevated baseline activated partial prothrombin times had elevations above the ULN during the 12 month study period were balanced by the proportion of patients with reduced baseline prothrombin with reductions below the LLN during the 12 month study period.

As discussed below, both ocular and systemic AEs reflecting the prespecified RMP safety concerns occurred more frequently in patients taking concomitant anticoagulant medicines compared with patients not taking anti-coagulant medicines in both the sham and combined ranibizumab groups in the 6 month treatment period.

Chemistry

In ***BRAVO***, elevated glucose levels above the ULN during the 12 month study period in patients with normal baseline levels were reported in 23.7% (22/93) of patients in the 0.3 mg group and 19.4% (19/98) in the 0.5 mg group. There were only three other laboratory chemistry parameters with levels above the ULN in > 3% of patients with normal baseline levels in both the ranibizumab treatment groups (0.3 mg vs 0.5 mg) in the 12 month study period: ALT (3.9% [4/102] vs 4.4% [5/114]); AST (3.8% [4/104] vs 6.1% [7/115]; and uric acid (3.7% [4/109] vs 6.8% [8/117]). There were no laboratory chemistry parameters below the LLN in > 3% of patients with normal baseline levels in both ranibizumab treatment groups in the 12 month study period.

In ***CRUISE***, elevated glucose levels above the ULN during the 12 month study period in patients with normal baseline levels were reported in 14.6% (14/96) of patients in the 0.3 mg group and 14.0% (13/93) in the 0.5 mg group). There were only two other laboratory chemistry parameters with levels above the ULN in ≥ 3% of patients with normal baseline levels in both the ranibizumab treatment groups (0.3 mg vs 0.5 mg) in the 12 month study period: alanine aminotransferase (ALT) (5.1% [6/117] vs 4.8% [5/103]); and uric acid (3.6% [4/111] vs 4.0% [4/101]). There were no chemistry parameters below the LLN in ≥ 3% of patients with normal baseline levels in both ranibizumab treatment groups in the 12 month study period.

In the pooled chemistry data, 1 patient experienced a SAE (hyponatraemia in the 0.3 mg group). No patients were discontinued due to laboratory abnormalities.

Evaluator Comment

In both studies, the most commonly occurring laboratory chemistry abnormality in the 12 month study period was elevated glucose levels. This abnormality occurred in 14.3% and 21.5% of patients with normal baseline levels in the combined ranibizumab group in CRUISE and BRAVO, respectively. However, in only 2 patients in the combined

ranibizumab group (0.4% [2/525]) was increased blood glucose reported as an AE in the 12 month study period. Increased blood glucose is not identified in the currently approved PI. *Nevertheless, the findings in the two pivotal RVO studies are of concern and comment should be requested from the sponsor.*

Increased ALT levels above the ULN in the 12 month study were reported in both studies (~ 4% to 5% of patients with normal baseline levels) but no data on the degree of elevation above the ULN could be identified in the submitted data. However, hepatic toxicity does not appear to be significant clinical issue with ranibizumab. Only 1 patient in the combined ranibizumab group (0.2% [1/525]) was reported to have increased hepatic enzymes as an AE in the 12 month study period. Overall, hepatobiliary AEs were reported in 2 patients in the sham treatment group (1 x cholelithiasis, 1 x cholecystitis, 1 x hepatomegaly) and 3 patients (0.6%) in the combined ranibizumab group (cholelithiasis, cholecystitis, hepatic cirrhosis). Uric acid was the only other chemistry parameter elevated above the ULN in both studies in ≥ 3% of patients in the 12 month study period (~ 3.5% to 7.0% of patients with normal baseline levels). No patients could be identified with elevated uric acid as an AE.

Urinalysis

In both ***BRAVO*** and ***CRUISE***, urinalysis abnormalities were reported as being infrequent in both treatment groups at Month 12. In both studies, the most common abnormality in qualitative urinalysis was a mild elevation in protein in the urine. In ***BRAVO***, among patients who had a negative result for urine protein at baseline, 11.5% in the 0.3 mg group and 17.7% in the 0.5 mg group had urine protein measured as either trace or 1 + in the last post-baseline urine sample. In ***CRUISE***, among patients who had a negative result for urine protein at baseline, 26.7% in the 0.3 mg group and 12.8% in the 0.5 mg group had urine protein measured as either trace or 1 + in the last post-baseline urine sample.

Evaluator Comment

Proteinuria was noted very commonly (that is > 10%) in ranibizumab treated patients in both pivotal studies in the last post-baseline urine sample. However, no deterioration of renal function appears to have occurred in patients treated with ranibizumab. Furthermore, no AEs identified as proteinuria were reported in the pivotal studies. *Nevertheless, the sponsor should be requested to comment on the findings of proteinuria.* Proteinuria was identified in the RMP as an important potential risk with ranibizumab treatment.

Ranibizumab antibodies

Serum samples for evaluation of antibodies to ranibizumab were obtained at screening, Month 6 and Month 12 (or earlier in the case of discontinuation). Of the patients with evaluable samples at baseline, 3.5% (9/256), 2.7% (7/258) and 3.2% (8/252) tested positive for antibodies to ranibizumab in the sham, 0.3 and 0.5 mg groups, respectively. The sponsor states that these findings might be possibly due to pre-existing anti-Fab antibodies [Süsal et al., 2000].[13] At month 12, 5 of 6 patients in the 0.3 mg were still antibody positive who had also been antibody positive at baseline, and the corresponding figures in the 0.5 mg group were 5 of 7 patients. Of the 224 patients in the 0.3 mg group who tested negative at baseline, 5 (2.2%) who were retested at month 12 were antibody positive, and the corresponding figures for the 0.5 mg group were 4 (1.8%) patients positive out of the 220 who were negative at baseline. The sponsor concluded that

[13] Süsal C, Döhler B, Opelz G. Graft-protective role of high pretransplantation IgA–anti-Fab autoantibodies: confirmatory evidence obtained in more than 4000 kidney transplants. The Collaborative Transplant Study. Transplantation; 2000: 69:1337-40.

changes in VA and AEs from baseline to Month 12 for antibody positive patients were consistent with the larger study population, with no clinically relevant differences in AEs between antibody positive and negative patients being identified.

Evaluator Comment

The antibody conversion rate in the pooled ranibizumab was small (2.0% [9/444]). Although the sponsor concluded that there were no relevant differences in VA and AEs between antibody positive and antibody negative patients, it is considered that the number of antibody positive patients was too small to allow clinically meaningful comparisons between the two patient groups to be made.

Vital Signs

Vital sign measurements (blood pressure, pulse rate, temperature, respiration rate) were taken at screening, prior to dosing at each monthly visit during the 6 month treatment period, and at each monthly visit during the 6 month observation period. In the 6 month treatment period and the 12 month study period, there were no clinically meaningful changes from baseline in pulse rate, temperature and respiration in the treatment groups. However, in the 6 month treatment period, hypertension (> 150/100 mmHg) was reported in 35.7% (n=92), 38.3% (n=101) and 35.9% (n=92) of patients in the sham, 0.3 mg and 0.5 mg groups, respectively, and the corresponding figures for severe hypertension (>200/110 mmHg) were 1.2% (n=3), 1.1% (n=3) and 0.8% (n=2). In the 12 month study period, hypertension (>150/100 mmHg) was reported in 44.2% (n=230) of patients in the combined ranibizumab group, and the corresponding figure for severe hypertension (>200/110 mmHg) was 1.2% (n=3).

Special Ocular Examinations

Slit Lamp Examination

Slit lamp examination was performed on Days 0 and 7 and at each monthly visit during the treatment and observation periods.

Intraocular Inflammation (most severe aqueous cell, aqueous flare, or vitreous cell inflammation observed for each patient across all post baseline assessment):

In the 6 month treatment period, 8.8% (n=23) of sham treated patients were reported to have at least trace intraocular inflammation in the study eye at 1 or more slit lamp examinations compared with 4.9% (n=13) in the 0.3 mg group and 2.7% (n=7) in the 0.5 mg group. Only one patient (0.5 mg group) had intraocular inflammation of Grade 2 + in the study eye reported during the 6 month treatment period. In the 12 month study period, 4.4% (n=23) of patients in the combined ranibizumab group were reported to have at least trace intraocular inflammation in the study eye at 1 or more slit lamp examinations, and only one patient (0.5 mg group) had intraocular inflammation of Grade 2 +. Intraocular inflammation was reported as an AE in the study eye in the 6 month treatment period in 11.5% of patients in the sham group and 9.1% of patients in the combined ranibizumab group, and 20.2% of patients in the combined ranibizumab group in the 12 month study period.

Vitreous haemorrhage

In the 6 month treatment period, vitreous haemorrhage with a grade of trace or higher on slit lamp examination occurred in 6.9% (n=18) of patients in the sham group compared with 5.3% (n=14) in the 0.3 mg group and 4.7% (n=12) in the 0.5 mg group. Vitreous haemorrhage in the study eye with a Grade of 2+ or higher was observed in 5 patients (1.9%) in the sham group compared with no patients in the ranibizumab groups. In the 12 month study period, 5.5% (n=29) of patients in the combined ranibizumab group were

reported to have at least trace intraocular inflammation in the study eye at 1 or more slit lamp examinations, and only one patient (0.3 mg group) had intraocular inflammation of Grade 2 +.Vitreous haemorrhage was reported as an AE in the study eye in the 6 month treatment period in 5.8% of patients in the sham group and 3.8% of patients in the combined ranibizumab group, and 4.4% of patients in the combined ranibizumab group in the 12 month study period.

Iris neovascularization

In the 6 month treatment period, iris neovascularization (any) on slit lamp examination was reported in 4.6% (n=12) of patients in the sham group compared with 1.1% (n=3) in the 0.3 mg group and 1.5% (n=4) in the 0.5 mg group, and in 2.9% (n=15) of patients in the combined ranibizumab group during the 12 month study period. Iris neovascularization was reported as an AE in the 6 month treatment period in 4.6% (n=12) patients in the sham group compared with 0.8% (n=2) in the 0.3 mg group and 0.4% (n=1) in the 0.5 mg group, and in 1.7% (n=9) of patients in the combined ranibizumab group during the 12 month study period.

Intraocular Pressure (IOP)

IOP was assessed at screening, before dosing and 1 hour following dosing on Days 0 and 7, before dosing (both eyes) and 1 hour following dosing (study eye only) at subsequent monthly treatment visits during the treatment period, and at each monthly visit during the observation period. At baseline (before dosing on Day 0), the mean IOP in the study eye was approximately 14.9 mmHg (range: 6–28 mmHg) in the safety evaluable population, and the mean IOP was similar across the treatment groups.

In the *6 month treatment period*, increases of ≥ 10 mmHg in IOP in the study eye compared with baseline were reported in 0.9% (2/232), 1.2% (3/250) and 1.7% (4/234) of patients in the sham, 0.3 mg and 0.5 mg treatment groups, respectively. The incidence of any post-baseline increase in IOP ≥ 30 mmHg during the 6 month treatment period in the study eye was 2.7% (7/260), 5.3% (14/266) and 5.0% (13/259) of patients in the sham, 0.3 mg and 0.5 mg treatment groups, respectively. On average, post-dose IOP (that is, one hour after treatment) was elevated by approximately 3 to 4 mmHg in the study eye in the ranibizumab groups compared with 1 to 2 mmHg in the sham group. The incidence of any post-dose increase in IOP ≥ 30 mmHg during the 6 month treatment period in the study eye was 1.9% (5/260), 5.3% (14/266), and 5.0% (13/258 of patients in the sham, 0.3 mg and 0.5 mg treatment groups, respectively. In the *12 month study period*, the incidence of any post-baseline IOP increase ≥ 30 mmHg in the study eye was 8.6% (45/525) in the combined ranibizumab group (9.0% and 8.1% in the 0.3 and 0.5 mg groups, respectively), and corresponding figures for any post-dose IPO increase of ≥ 30 mmHg in the study eye were 7.8% (41/254) in the combined ranibizumab group (8.6% and 7.0% in the 0.3 and 0.5 mg groups, respectively).

Glaucoma as an AE in the 6 month study period in the study eye was reported in 6 (2.3%) patients in the sham group, no patients in the 0.3 mg group and 2 (0.8%) patients in the 0.5 mg group. In the 12 month study period, glaucoma in the study eye was reported in 4 patients (1.5%; 4 AEs) in the 0.3 mg group and 6 patients (2.3%; 9 AEs) in the 0.5 mg group. One patient in the 0.5 mg group with glaucoma in the 12 month treatment period discontinued due to the event.

Evaluator Comment

Increases in IOP occurred more frequently in ranibizumab treated patients that sham treated patients. This is a known effect following IVT injections. Glaucoma was reported infrequently in the 6 month treatment period in the three treatment groups.

Retinal ischaemia

Retinal ischaemia was defined by the total capillary loss in the centre subfield as the percentage of the area of the centre subfield (that is, 0% = no ischaemia; 30% = mild; > 30% to 60% = moderate; > 60% to < 100% = severe; 100% = completely destroyed). No patient in the study had retinal ischaemia classified as "completely destroyed". At baseline, the percentage of patients with no retinal ischaemia was similar in the three treatment groups: sham (79.5% [186/234]); 0.3 mg (78.2% [186/266]) and 0.5 mg (80.9% [182/225]). At Month 6, the frequency of patients with no retinal ischaemia was higher in both 0.3 mg and 0.5 mg groups than the sham group (79.8% [152/203], 77.9%, [158/203] and 67.0% [136/203], respectively. The percentage of patients in the pooled ranibizumab group (0.3 plus 0.5 mg) with no ischaemia at baseline was higher at baseline than at Month 12 (79.5% [368/463] vs 73.3% [291/397], respectively).

APTC arterial thromboembolic events

Both pivotal studies included an assessment of Antiplatelet Trialists' Collaboration (APTC) arterial thromboembolic events (vascular deaths, non-fatal MIs, non-fatal ischaemic CVAs, and non-fatal haemorrhagic CVAs) [APTC, 1994]. In ***BRAVO,*** *in the 6 month treatment period* APTC arterial thromboembolic events occurred in 1 (0.8%) patient in sham group (non-fatal haemorrhagic CVA) and 2 (1.5%) patients in the 0.5 mg group (non-fatal MI, fatal haemorrhagic CVA). *In the 12 month study period*, APTC arterial thromboembolic events occurred in 1 (0.7%) patient in the 0.3 mg group (embolic stroke) and 2 (1.5%) patients in the 0.5 mg group (acute MI, cerebral haemorrhage). In addition, 1 (0.9%) patient in the sham/0.5-mg group treated with ranibizumab experienced an MI during the 6 month observation period.

In ***CRUISE***, during the 6 month treatment period 1 (0.8%) patient in the sham group, 1 (0.8%) in the 0.3 mg group, and 1 (0.8%) in the 0.5 mg group each experienced one APTC arterial thromboembolic event (non-fatal MI). *In the 12 month study period*, APTC arterial thromboembolic events occurred in 1 (0.8%) patient in the 0.3 mg group (MI) and 3 (2.3%) patients in the 0.5 mg group (CVA, MI, death of unknown cause). There were no ATPC events in the sham/0.5 mg group in the 6 month observation period.

Evaluator Comment

In both studies, the 6 month treatment data showed no notable differences in APTC arterial thromboembolic events between the sham and ranibizumab groups. Overall, the number of APTC arterial thromboembolic events in both studies was small and suggests no significant association with ranibizumab.

Ocular adverse events in the non-study (fellow) eye

In ***BRAVO***, *in the 6 month treatment period* ocular AEs in the fellow eye occurred in 22.1% (29/131), 29.9% (40/134) and 25.4% (33/130) of patients in the sham, ranibizumab 0.3 mg and ranibizumab 0.5 mg groups respectively. Ocular AEs occurring in ≥ 2% of patients in the fellow eye were (sham vs 0.3 mg vs 0.5 mg): dry eye (0.8% [n=1] vs 2.2% [n=3] vs 2.3% [n=3]); raised intraocular increased (0.8% [n=1] vs 0% vs 3.1% [n=4]); maculopathy (1.5% [n=2] vs 1.5% [n=2] vs 3.8% [n=5]); ocular vascular disorder (3.1% [n=4] vs 5.2% [n=7] vs 0%); retinal exudates (1.5% [n=2] vs 2.2% [n=3] vs 1.5% [n=2]); retinal haemorrhage (1.5% [n=2] vs 5.2% [n=7] vs 4.6% [n=6]); and vitreous detachment (0.8% (n=1] vs 3.0% [n=4] vs 0.8% [n=1]). *In the 12 month study period*, 39.4% (104/264) of patients treated with ranibizumab experienced an ocular AE in the fellow eye. Ocular AEs occurring in the fellow eye in ≥ 2 % of patients were retinal haemorrhage (7.6% [n=20]), dry eye (4.9% [n=13]), maculopathy (4.5% [n=12]), retinal vascular disorder (3.8% [n=10]), retinal exudates (3.8% [n=10]), macular degeneration (3.0% [n=8]), increased

intraocular pressure (3.0% [n=8]), cataract (2.3% [n=6]), and retinal aneurysm (2.3% [n=6]).

In ***CRUISE***, *in the 6 month treatment period* ocular AEs in the fellow eye occurred in 24.0% (31/129), 17.4% (23/132) and 31.0% (40/129) of patients in the sham, ranibizumab 0.3 mg and ranibizumab 0.5 mg groups respectively. Ocular AEs occurring in ≥ 2% of patients in the fellow eye were (sham vs 0.3 mg vs 0.5 mg): maculopathy (3.1% [n=4] vs 1.5% [n=2] vs 3.9% [n=5]); retinal exudates (2.3% [n=3] vs 0.8% [n=1] vs 2.3% [n=3]); retinal haemorrhage (3.1% [n=4] vs 2.3% [n=3] vs 4.7% [n=6]); retinal vascular disorder (3.1% [n=4] vs 3.0% [n=4] vs 3.9% [n=5]); retinal vein occlusion (0.8% [n=1] vs 2.3% [n=3] vs 3.9% [n=5]); and vitreous detachment (2.3% [n=3] vs 0% vs 2.3% [n=3]. *In the 12 month study period,* 35.2% (92/261) of patients treated with ranibizumab experienced an ocular AE in the fellow eye. Ocular AEs occurring in the fellow eye in ≥ 2 % of patients in the combined ranibizumab group were retinal haemorrhage (5.4% [n=14]), retinal vascular disorder (5.4% [n=14]), maculopathy (4.6% [n=12]), vitreous detachment (3.5% [n=9]), retinal vein occlusion (3.4% [n=9]), retinal exudates (3.1% [n=8]), increased intraocular pressure increased (2.3% [n=6]), dry eye (2.3% [n=6]), and blepharitis (2.3% [n=6]).

Evaluator Comment

In both studies, ocular AEs in the fellow eye occurred more commonly in one or both of the ranibizumab treatment groups than in the sham group in the 6 month treatment period. Ocular AEs occurred more frequently in the 0.5 mg group than in the 0.3 mg group in the 6 month treatment period in CRUISE with the reverse relationship being observed in BRAVO.

In BRAVO, ocular AEs in the fellow eye occurred more frequently in both ranibizumab treatment groups than in the sham treatment group in the 6 month treatment period. In addition, ocular AEs in the fellow eye occurring with an incidence of ≥ 2% in any treatment group were all reported more commonly in one or both of the ranibizumab dose groups compared with the sham group. The most commonly reported events in any treatment group were ocular vascular disorder and retinal haemorrhage (both reported with an incidence of 5.2% [n=7] in the 0.3 mg group). In the 12 month study period, the pattern of ocular AEs in the fellow eye in BRAVO were generally consistent with that in the 6 month treatment period, but with events occurring marginally more frequently at 12 months compared with 6 months.

In CRUISE, ocular AEs in the fellow occurred more commonly in the sham group than in the 0.3 mg group, but less commonly in the sham group than in the 0.5 mg group in the 6 month treatment period. This pattern was also generally observed for individual ocular AEs occurring with an incidence of ≥ 2% in any treatment group. The most commonly reported event in any treatment group was retinal haemorrhage (4.7% [n=6] in the 0.5 mg group). In the 12 month study period, the pattern of ocular AEs in the fellow eye in BRAVO were generally consistent with that in the 6 month treatment period, but with events occurring marginally more frequently more frequently at 12 months compared with 6 months.

Other safety issues

Safety in special populations

Gender (intrinsic factor)

In the *6 month treatment period*, the incidence of ocular AEs (male vs female patients) reflecting prespecified RMP safety concerns was 29.9% (43/144) vs 32.8% (38/116) in the sham group, and 31.0% (89/287) vs 31.5% (75/238) in the combined ranibizumab

group. In the *12 month study period*, the corresponding values in the combined ranibizumab group were 52.3% (150/287) in males and 51.3% (122/238) in females.

In the *6 month treatment period*, the incidence of systemic AEs (male vs female patients) reflecting prespecified RMP safety concerns was 20.1% (29/144) vs 21.6% (25/116) in the sham group and 18.1% (52/287) vs 16.0% (38/238) in the combined ranibizumab group. In the *12 month study period*, the corresponding values in the combined ranibizumab group were 26.1% (75/287) in males and vs 24.4% (58/238) in females.

Age (intrinsic factor)

In the *6 month treatment period*, the incidence of patients with any ocular AE (< 65 vs ≥ 65 years) reflecting prespecified RMP safety concerns was 27.8% (35/126) vs 34.3% (46/134) in the sham group and 31.7% (64/202) vs 31.0% (100/323) in the combined ranibizumab group. The AE profiles did not markedly differ between the younger and older ranibizumab treated patients. In the *12 month study period*, the corresponding values in the combined ranibizumab group were 53.5% (108/202) in the < 65 years group and 50.8% (164/323) in the ≥ 65 years group. There were 2 ocular AEs that occurred ≥ 2% more frequently in younger (>65 years) than older (≥65 years) ranibizumab treated patients in the 12 month study period: intraocular inflammation (22.8% vs 18.6%); and deterioration of retinal blood flow (29.2% vs 23.2%).

In the *6 month treatment period*, the incidence systemic AE (patients aged < 65 vs aged ≥ 65 years) reflecting prespecified RMP safety concerns was 22.2% (28/126) vs 19.4% (26/134) in the sham group and 17.8% (36/202) vs 16.7% (54/323) in the combined ranibizumab group. In both the sham and combined ranibizumab groups, the incidence of hypertension occurred ≥ 2% more frequently in younger age (< 65 years) than older (≥ 65 years) patients. In the combined ranibizumab group, "other" arterial thromboembolic events occurred ≥ 2% more frequently in older (≥ 65 years) than in younger (< 65 years) patients (2.2% vs 0%). In the *12 month study period*, the incidence of systemic AEs reflecting prespecified RMP safety concerns was 25.2% (51/202) in patients aged < 65 years and 25.4% (82/323) in patients aged ≥ 65 years. In the combined ranibizumab group, hypertension occurred ≥ 2% more frequently in younger (<65 years) than in older (≥ 65 years) patients (13.4% vs 11.1%). Conversely, in the combined ranibizumab group "other" arterial thromboembolic events occurred ≥ 2% more frequently in older (≥ 65 years) than younger patients (3.4% vs 0%).

Race (intrinsic factor)

No assessment of safety based on race could be identified in the submission. The majority of patients in the sham, ranibizumab 0.3 mg and ranibizumab 0.5 mg safety evaluable patients were White (84.6%, 82.7%, and 83.0%, respectively) and the next most common racial group was Black (~ 8% to 10%). Consequently, due to the imbalance between racial group numbers it would be difficult to make clinically meaningful safety comparisons based on race.

Other intrinsic factors

Baseline blood pressure

Safety evaluable patients were categorised has having high baseline blood pressure (≥150 mmHg) or low baseline pressure (<150 mmHg); it is assumed that the blood pressure criteria related to baseline systolic blood pressure but this could not be confirmed in the submitted data. Overall, ocular and systemic AEs reflecting the prespecified RMP safety concerns in patients with high and low blood pressure in the combined ranibizumab group in the 12 month study period were generally similar, apart from a notably higher

risk of systemic hypertension in patients with high baseline blood pressure compared with patients with low baseline blood pressure (23.1% [24/104] vs 9.3% [39/421]).

Time since diagnosis of RVO

In the combined ranibizumab group, ocular and systemic AEs in the 12 month study period reflecting RMP safety concerns were similar in patients with RVO ≤ 3 months and > 3 months before diagnosis.

Baseline history of ischaemia

The submission included a comparison of safety in patients with and without baseline retinal ischaemia in the combined ranibizumab group. However, it is considered that no meaningful comparison can be made between the two groups because of the marked numerical imbalance in the combined ranibizumab group between patients without (n=438) and with baseline retinal ischaemia (n=25) (that is, 17.5 fold more patients without retinal ischaemia than with retinal ischaemia).

Baseline history of cardiovascular disease (CVD)

In the 12 month study period, ocular and systemic AEs reflecting the prespecified RMP safety concerns generally occurred with similar frequencies in patients with and without a baseline history of CVD in the combined ranibizumab group, with the exceptions being systemic hypertension and hypersensitivity. Systemic hypertension occurred more frequently in patients with a history of baseline CVD than in patients without a history of baseline CVD (17.6% vs 11.2%), while hypersensitivity occurred more frequently in patients without a history of baseline CVD than in patients with a history of baseline CVD (11.2% vs 5.9%). The differences between the two groups should be interpreted cautiously due to the numerical imbalance between patients with a history of CVD (n=457) compared with patients without a history of cardiovascular disease (n=68) in the combined ranibizumab group (that is, 6.7 fold more patients without baseline CVD than with baseline CVD.

Baseline history of glaucoma

In the 12 month study period, ocular and systemic AEs reflecting the prespecified RMP safety concerns generally occurred with similar frequencies in patients with and without a baseline history of glaucoma, with exceptions of systemic hypertension and increased intraocular pressure. Systemic hypertension occurred more commonly in patients without a history of glaucoma compared with patients with a history of glaucoma (13.3% vs 4.9%), while patients with a history of glaucoma had a higher incidence of raised intraocular pressure than patients without a history of glaucoma (22.0% vs 10.2%). The differences between the two groups should be interpreted cautiously due to the numerical imbalance between patients with a history of glaucoma (n=443) compared with patients without a history of glaucoma (n=82) in the combined ranibizumab group (that is, 5.4 fold more patients with a history of glaucoma compared with patients with a history of glaucoma).

Extrinsic factors

Concomitant use of anticoagulant drugs

In the 6 month treatment period, ocular AEs reflecting prespecified RMP safety concerns occurred more commonly in patients taking anticoagulants compared with patients not taking anticoagulants in both the sham group (54.4% vs 29.0%) and combined ranibizumab group (25.0% vs 31.8%). Intraocular inflammation and deterioration of retinal blood flow both occurred more commonly in patients taking concomitant anticoagulants in both the sham and ranibizumab treatment groups. In the 6 month treatment period, systemic AEs reflecting the prespecified RMP safety concerns occurred

more commonly in patients taking anticoagulants than in patients not taking anticoagulants in both the sham (31.8% vs 19.7%) and the combined ranibizumab group (27.3% vs 16.2%). The most notable difference between patients taking and not taking concomitant anticoagulants in both the sham and combined ranibizumab groups was the higher incidence of non-ocular haemorrhages in patients taking concomitant anticoagulants. However, the observed differences should be interpreted cautiously in both the sham and ranibizumab groups as in both treatment groups patients not taking concomitant anticoagulants outnumbered those taking concomitant anti-coagulants by about 11 fold.

Concomitant treatment laser treatment

BRAVO (but not ***CRUISE***) included a comparison of ocular AEs reflecting prespecified RMP safety concerns in patients treated with and without concomitant laser treatment according to the number of injections received. Concomitant laser treatment was defined if occurring within 30 days before injection of study drug and only AEs that occurred within 14 days of injection were included in the analysis. In patients treated with concomitant laser treatment, ocular AEs occurring more commonly in at least one of the ranibizumab mono treatment groups (0.3 mg or 0.5 mg) than in the sham mono group at 12 months (sham vs 0.3 mg vs 0.5 mg) were: intraocular inflammation (3.6% [4/112 injections), 7.6% [7/92 injections], 4.9% [6/122 injections]); and raised intraocular pressure (0.9% [1/112 injections] vs 2.2% [2/92 injections] vs 2.5% [3/122 injections]). Conversely, deterioration of retinal blood flow occurred more commonly in the sham mono group treated with concomitant laser than in the 0.3 mg mono group and the 0.5 mono group (5.4% [6/112 injections] vs 4.3% [4/92 injections] vs 4.1% [5/122 injections], respectively), as did vitreous haemorrhage (0.9% [1/112 injections vs 0% both ranibizumab groups). In patients without laser treatment, the only ocular AE of note which occurred with notably different frequencies among the three treatment groups was increased intraocular pressure which occurred more commonly in patients treated with 0.3 mg (2.1% [22/1052]) and 0.5 mg (1.5% [21/1445 injections]) ranibizumab than in sham treated patients (0.5% [3/620 injections].

Evaluator Comment

Ocular AEs reflecting RMP safety concerns in patients given concomitant laser treatment occurred in a small number of patients in both the sham and ranibizumab treatment groups. Of note was the increased incidence of intraocular inflammation in concomitant ranibizumab and laser treated patients compared with concomitant sham and laser treated patients, and, conversely, the increased incidence of deterioration of retinal blood flow in concomitant sham and laser treated patients compared with concomitant ranibizumab and laser treated patients. Overall, the available data do not raise significant safety concerns associated with concomitant ranibizumab and laser treatment in patients with RVO.

Evaluator's overall conclusions on clinical safety

The safety of ranibizumab in patients with RVO was evaluated in two, pivotal 12 month studies. In the pooled safety data, 525 patients with RVO were exposed to ranibizumab for 12 months (266 at the 0.3 mg dose and 259 at the 0.5 mg dose). There was no marked difference between the incidence of AEs in the 0.3 mg and 0.5 mg ranibizumab groups in either the 6 month treatment period or the 12 month study period. The safety profiles of the two ranibizumab dose groups were similar and no consistent clinically meaningful dose response relationship was observed. There were no safety data in patients with RVO treated with ranibizumab for more than 12 months and this is a deficiency in the submission. It is noted that a long term extension study has been completed [FVF3426g]

and this study should be provided to the TGA as soon as the CSR has been finalized. Overall, the safety profile of ranibizumab in patients with RVO was consistent with that known for patients with wet-AMD. It is considered that the submitted data have satisfactorily established the safety of ranibizumab 0.5 mg for the proposed indication. Unless otherwise stated, the safety outcomes discussed below relate to the pooled data from the safety evaluable population in both pivotal studies.

There were 5 deaths in the two pivotal studies and 2 deaths in extension study and 1 of the deaths in ***BRAVO*** (respiratory failure preceded by cerebral haemorrhage in a 78 year old male) was considered by the investigator to be related to the study drug.

Ocular AEs in the study eye in the 6 month treatment period were reported more frequently in patients in the ranibizumab 0.3 mg and 0.5 mg groups than in the sham group (80.8% [215/266], 81.1% [210/259] and 76.9% [200/260], respectively). The increased risk of ocular AEs with IVT ranibizumab injections compared with sham non-penetrating injections is not unexpected. In the 12 month study period, ocular AEs in the study eye were reported in 90.2% (240/266) and 88.4% (229/259) of patients in the ranibizumab 0.3 and 0.5 mg treatment groups, respectively.

Non-ocular AEs in the 6 month treatment period were reported with similar frequencies in patients in the sham, 0.3 mg and 0.5 mg treatment groups (51.5% [134/260], 52.6% [140/266] and 52.9% [137/259], respectively). In the 12 month study period, non-ocular AEs were reported in 72.9% (194/266) and 67.2% (174/259) of patients in the 0.3 mg and 0.5 mg groups, respectively.

The most frequently reported ocular AE in the study eye in the 6 month treatment period was conjunctival haemorrhage, which was reported in 49.7% of patients in the combined ranibizumab group and 37.3% of patients in the sham group. Other ocular AEs in the study eye occurring in ≥ 5% of patients in the combined ranibizumab group and more frequently than in the sham group in the 6 month treatment period were retinal exudates (23.4% vs 12.7%), eye pain (17.0% vs 12.3%), maculopathy (12.2% vs 7.3%), retinal vascular disorder (11.8% vs 9.2%), retinal haemorrhage (11.6% vs 11.2%), maculopathy (12.2% vs 7.3%), myodesopsia (8.4% vs 2.3%), retinal depigmentation (7.6% vs 4.2%), foreign body sensation in the eye (7.2% vs 5.0%), increased intraocular pressure (6.7% vs 2.3%), ocular vascular disorder (6.5% vs 5.0%) and ocular hyperaemia (5.9% vs 2.7%). Most ocular AEs in the study eye occurring in the 6 month treatment period were categorized as non-severe, and ocular severe AEs occurred more commonly in the sham group (3.8% [n=10]) than in the combined ranibizumab group (2.7% [n=14]).

Ocular SAEs (any) in the study eye in the 6 month treatment period were infrequent and were reported in 3.1% (n=8) of patients in the sham group and 2.1% (n=11) of patients in the combined ranibizumab group. The only individual ocular SAE in the study eye occurring in ≥ 1% of patients was macular oedema which was reported in 1.2% (n=3) of patients in the sham group compared with 0.4% (n=2) of patients in the combined ranibizumab group. Discontinuations due to ocular AEs in the study eye in the 6 month treatment period were infrequent and were reported in 1.9% (n=5) of patients in the sham group and 0.4% (n=2) of patients in the combined ranibizumab group. The ocular AEs resulting in discontinuation in the 6 month treatment period in the 5 patients in the sham group were macular oedema (2), retinal vein occlusion (2), iris neovascularization (1) and macular ischaemia (1), and in the 2 patients in the combined ranibizumab group were corneal oedema (1) and endophthalmitis (1).

Ocular AEs in the study eye occurring in ≥ 10% of patients in the combined ranibizumab group (n=525) in the 12 month study period were conjunctival haemorrhage (52.2%), retinal exudates (29.0%), retinal haemorrhage (25.0%), maculopathy (21.3%), retinal

vascular disorder (20.6%), eye pain (19.6%), macular oedema (11.8%), retinal depigmentation (10.7%) and myodesopsia (10.7%). Most ocular AEs occurring in the 12 month treatment period were categorized as non-severe and ocular severe AEs occurred in only 3.6% of patients in the combined ranibizumab group.

Ocular SAEs (any) in the study eye in the 12 month study period were reported in 4.0% (n=21) of patients in the combined ranibizumab group. There were a total of 16 different ocular SAEs reported in the study eye during the 12 month period. The only ocular SAEs reported in the study eye occurring in more than 1 patient in the combined ranibizumab group were macular oedema (n=7 [1.3%]) and retinal vein occlusion (n=4 [0.8%]). In the 12 month study period, ocular AEs in the study eye resulting in discontinuation occurred in 1 (0.4%) patient in the 0.3 mg group (corneal oedema), and 2 patients (0.8%) in the 0.5 mg group (endophthalmitis, glaucoma, iris neovascularization).

Ocular AEs in the study eye of special interest noted in the RMP and considered to reflect important identified and potential risks with ranibizumab treatment are deterioration of retinal blood flow, intraocular inflammation, increased intraocular haemorrhage, vitreous haemorrhage, traumatic cataract, retinal tear, retinal detachment and endophthalmitis. The risk of patients experiencing at least one of these key ocular AEs in the 6 month treatment period was identical in the sham and combined ranibizumab groups (31.2% [n=81] vs 31.2% [n=164], respectively). Key ocular AEs occurring more frequently in patients in the combined ranibizumab group than in the sham group were raised intraocular pressure (7.0% vs 3.8%), retinal tear (0.6% vs 0%), and endophthalmitis (0.2% vs 0%). In the 12 month study period, the risk of patients experiencing at least one of these key ocular AEs was 51.8% (n=272) in the combined ranibizumab group, with three events occurring in ≥ 10% of patients (deterioration of retinal blood flow [25.5%], intraocular inflammation [20.2%] and increased IOP [12.0%]).

Non-ocular AEs (any) in the 6 month treatment period were reported with similar frequencies in patients in the sham and combined ranibizumab groups (51.5% [n=134] and 52.8% [n=277], respectively). However, the majority of these events were reported in < 5% of patients in both of these treatment groups. The only non-ocular AEs reported in ≥ 5% of patients in the combined ranibizumab group (vs sham) were hypertension (5.5% vs 8.1%) and nasopharyngitis (5.3% vs 3.8%). In the 12 month study period, 70.1% (n=368) of patients in the combined ranibizumab group experienced at least one non-ocular AE, with three events occurring in ≥ 5% patients (hypertension [9.9%], nasopharyngitis [7.6%] and sinusitis [6.7%]).

Non-ocular SAEs (any) in the 6 month treatment period were reported more frequently in the combined ranibizumab group than in the sham group (8.8% [n=46] and 5.8% [n=15], respectively). However, in neither of these treatment groups were individual non-ocular SAEs reported in more than 2 patients. Non-ocular SAEs reported in 2 patients in the combined ranibizumab group but less than 2 patients in the sham group were cellulitis (2 [0.4%] vs 0), colitis (2 [0.4%] vs 0), hypertension (2 [0.4%] vs 1 [0.4%]), MI (2 [0.4%] vs 0), pneumonia (2 [0.4%] vs 1 [0.4%]), small intestinal obstruction (2 [0.4%] vs 0) and syncope (2 [0.4%] vs 0). In the 12 month study period, non-ocular SAEs were reported in 13.1% (n=69) of patients in the ranibizumab group, and the only event occurring in ≥ 1% of patients was pneumonia (1.0%).

Non-ocular AEs resulting in discontinuation in the 6 month treatment period occurred infrequently (0.8% (n=2) and 1.0% (n=5) of patients in the sham group and combined ranibizumab group, respectively). Of the 5 non-ocular AEs resulting in discontinuations in the combined ranibizumab group, 3 were related to cardiovascular disease (MI, arteriosclerosis coronary artery, cerebral haemorrhage), compared with none of the 2 non-ocular AEs resulting in discontinuation in the sham group. In the 12 month study

period, non-ocular AEs resulting in discontinuation occurred in 1.1% (n=6) patients in the combined ranibizumab group and 4 of the 7 reported individual events in the 6 patients were cardiovascular in origin.

Systemic AEs of special interest noted in the RMP and considered to reflect important identified and potential risks with ranibizumab treatment are hypersensitivity, hypertension, non-ocular haemorrhage, proteinuria, MI, other arterial thromboembolic events and venous thromboembolic events. In addition to non-ocular AEs, these systemic AEs also included ocular AEs (which appear to relate primarily to hypersensitivity reactions involving the study and/or fellow eye). Key systemic AEs (any) in the 6 month treatment period occurred more frequently in patients in the sham group than in patients in the combined ranibizumab group (20.8% [n=54] vs 17.1% [n=90]). There were two key systemic AEs reported in ≥ 5% of patients in both the combined ranibizumab and sham groups (hypersensitivity 8.2% vs 8.1%, respectively, and hypertension 6.7% vs 10.0%, respectively). Of the other key systemic AEs events, the only two reported more frequently in the combined ranibizumab group than in the sham group were MI (0.6% vs 0.4%) and other arterial events (1.3% vs 0.8%). In the 12 month study period, key systemic AEs occurred in 25.3% (n=133) of patients in the combined ranibizumab group, with three events occurring in ≥ 2% of patients (hypertension [12.0%], hypersensitivity [10.5%], and other arterial thromboembolic events [2.1%]).

APTC arterial thromboembolic events were investigated in both pivotal studies (vascular deaths, non-fatal MIs, non-fatal ischaemic CVAs, and non-fatal haemorrhagic CVAs). In ***BRAVO,*** in the 6 month treatment period APTC arterial thromboembolic events occurred in 1 (0.8%) patient in sham group (non-fatal haemorrhagic CVA) and 2 (0.8%) patients in the combined ranibizumab group (non-fatal MI, fatal haemorrhagic CVA). In the 12 month study period, APTC arterial thromboembolic events occurred in 1 (0.7%) patient in the 0.3 mg group (embolic stroke) and 2 (1.5%) patients in the 0.5 mg group (acute MI, cerebral haemorrhage). In ***CRUISE***, during the 6 month treatment period APTC arterial thromboembolic events occurred in 1 (0.8%) patient in the sham group (non-fatal MI) and 2 (0.8%) patients in the combined ranibizumab groups (both non-fatal MIs). In the 12 month study period, APTC arterial thromboembolic events occurred in 1 (0.8%) patient in the 0.3 mg group (MI) and 3 (2.3%) patients in the 0.5 mg group (CVA, MI, death of unknown cause).

Laboratory tests abnormalities giving rise to potential safety signals in ranibizumab treated patients were: reductions in haematocrit, haemoglobin levels and red blood cell counts; increased glucose levels; increased ALT levels; increased uric acid levels; and proteinuria. However, AE events related to these laboratory abnormalities were reported infrequently, if at all, and anaemia is a recognized AE that has been previously reported with ranibizumab. *Nevertheless, the sponsor should be requested to provide additional information on the laboratory findings relating to increased glucose, ALT and uric acid levels, and to proteinuria.*

The antibody conversion rate in ranibizumab treated patients was small (2.0% [9/444]). Although the sponsor concluded that there were no relevant differences in VA and AEs between antibody positive and antibody negative patients, it is considered that the number of antibody positive patients was too small to allow clinically meaningful comparisons between the two patient groups to be made.

Overall, there were no particular additional safety concerns associated with ranibizumab treatment in special groups and situations (intrinsic and extrinsic) as assessed by those AEs reflecting the identified and potential safety concerns noted in the RMP. However, patients with glaucoma should be closely monitored if treated with ranibizumab as the drug has been shown to increase intraocular pressure.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated. Some of these questions have been highlighted in the Clinical section.

Clinical questions

Efficacy

i. In both studies, patients were apparently prescribed self administered, post-injection antimicrobials. Please specify the nature of these antimicrobials and the treatment regimens used. Were the patients in the sham treatment groups prescribed either "post-injection" antimicrobials or placebo? If the sham treated patients did not receive either "post-injection" antimicrobials or placebo, please comment on the potential effect this has to bias the results between the ranibizumab and sham groups due to incomplete masking of treatments.

Sponsor Response:

To maintain masking all patients received antimicrobials. Throughout the protocol and in detail in Appendix E it is described: "The subject will be instructed to self administer antimicrobial drops (ofloxacin ophthalmic solution [ofloxacin ophthalmic solution, trimethoprim-polymyxin B ophthalmic solution, moxifloxacin ophthalmic solution or gatifloxacin ophthalmic solution single use vial]) four times daily for 3 days following each injection (ranibizumab or sham).

Evaluator Comment

The sponsor's response was satisfactory. No further action was required.

ii. In both pivotal studies, prior episodes of RVO were an exclusion criterion and the number of patients stated to have not met this criteria was low (n=4 pooled data). However, in ***BRAVO*** ~ 18% of patients had received prior treatment for RVO in the study eye, and in ***CRUISE*** the corresponding figure was ~ 14%. Please comment on this apparent discrepancy.

Sponsor Response

There were only two patients in the BRVO study (1 patient randomized to sham, 1 patient randomized to 0.3 mg ranibizumab) [BRAVO] who had a prior episode of RVO and reported as protocol deviations. There were also 2 patients in the CRVO study (1 randomized to sham, 1 randomized to 0.5 mg) [CRUISE] who had a prior episode of RVO and reported as protocol deviations.

According to the protocol, prior treatments with either laser, or anti-VEGF or triamcinolone were allowed with different periods before the randomization. Therefore patients have been treated for the same/current RVO episode that patients had at the time of the enrolment. The listings of the ocular/medical history and RVO duration confirm current events. Therefore for the current event in BRVO there were in total 71 (17.9%) patients with any prior RVO therapy [the response included a summary of the number of patients who received prior treatment for RVO and the nature of that treatment]. Consequently, although ~18% of patients in BRAVO and ~14% of patients in CRUISE received prior therapy for RVO, this prior treatment was for the same episode of RVO as was subsequently treated in the BRAVO or CRUISE study (that is, not a different, prior episode).

Evaluator Comment

The sponsor's response was satisfactory. No further action was required.

iii. In the 6 month observation period, patients were eligible for ranibizumab re-treatment if they met **either** of the following re-treatment criteria in the study eye: BCVA of 20/40 or worse (Snellen equivalent) using ETDRS charts; **or** mean central subfield thickness ≥ 250 µm on OCT. However, the proposed indication requires visual impairment due to macular oedema secondary to retinal vein occlusion (that is, decreased visual acuity **and** increased retinal thickness). Consequently, the re-treatment criteria do not appear to meet the proposed indication. Please justify the use of re-treatment criteria which required reduced visual acuity **or** increased mean central subfield thickness rather than **both** conditions. Please provide 12 month data for the primary efficacy outcome comparing results for patients who: (a) met only the re-treatment criterion of BCVA of 20/40 or worse (Snellen equivalent) using ETDRS charts; (b) who met only the re-treatment criterion of mean central subfield thickness ≥ 250 µm on OCT; and (c) who met both re-treatment criteria.

Sponsor Response

The re-treatment criteria that were used in studies FVF4165g and FVF4166g were not intended to mimic the proposed indication. Rather, they were designed to maximize the (maintenance) treatment effect. Measurements of central retinal thickness and visual outcomes have been shown to be poorly correlated at the level of the individual patient (Moutray et al 2008, Spaide et al 2006), therefore requiring a patient to have both BCVA of 20/40 or worse and CRT ≥ 250 µm in order to be re-treated would likely have resulted in under treatment during the 6 month observation period.[14,15]

A subgroup analysis of mean change from baseline in BCVA by re-treatment criterion as requested by the TGA would meet significant methodological problems. First, it will be difficult to assign patients to one of the three abovementioned groups because the same patient could have been re-treated for BCVA at Month 7, CRT at Month 9 and for both at Month 11. Second, differences in VA outcome between the three re-treatment groups will be confounded by a selection bias and do not necessarily reflect differences between the retreatment strategies that would have been found had the patients been randomized to them. By definition, patients who were re-treated for CRT ≥ 250 µm only had better vision than the two other groups even before re-treatment. The resulting subgroup differences at Month 12 could, therefore, be primarily due to the differences which already existed between the groups at the end of the 6 month treatment period. In view of these methodological problems, the sponsor did not believe the requested analysis would provide valuable information.

Evaluator Comment

The sponsor's response is satisfactory. No further action is required. The two publications referred to in the sponsor's response found no significant correlation between central retinal thickness and visual acuity. Consequently, outcomes based on improvements in visual acuity appear to be the most clinically relevant for assessment of the efficacy of IVT ranibizumab for the treatment of RVO. In a retrospective study of 266 patients (266 eyes) with choroidal neovascularization (CNV) secondary to age related macular degeneration [AMD], no significant correlation was noted between change in macular thickness and change in visual acuity during a 3 month treatment period with IVT bevacizumab (1.25 mg) [Spaide et al., 2006].[15] In a cross-sectional analysis in patients with exudative AMD

[14] Moutray T el al. Relationships between clinical measures of visual function, fluorescein angiographic and optical coherence tomography features in patients with subfoveal choroidal neovascularisation. Br J Ophthalmol 2008; 92: 361-364.

[15] Spaide RF et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 2006; 26: 383-390.

there were no statistically significant associations between optical coherence tomography (OCT) parameters of retinal thickness and foveal thickness and near (n=68) or distance (n=72) visual acuity [Moutray et al.,2008].[14] The sponsor's comments regarding the methodological problems of undertaking the proposed subgroup analysis were considered acceptable.

Safety

i. Please comment on the increased risk of ocular AEs in the fellow eye in patients with RVO treated with ranibizumab compared with sham. In both studies, ocular AEs in the fellow eye occurred more commonly in one or both of the ranibizumab treatment groups than in the sham group in the 6 month treatment period.

Sponsor Response

The following incidence rates regarding ocular events in the fellow eye were observed in the studies BRAVO and CRUISE during the 6-month study period [Table 19].

Table 19: Ocular adverse events in the fellow eye during the 6 month treatment period

Study	Parameter	Sham	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
BRAVO	Incidence rate	29/131 (22.1%)	40/134 (29.9%)	33/130 (25.4%)
	comparison to sham: 2-sided p-value (Fisher-Test)	-	0.1638	0.5633
CRUISE	Incidence rate	31/129 (24.0%)	23/132 (17.4%)	40/129 (31.0%)
	comparison to sham: 2-sided p-value (Fisher-Test)	-	*0.2221*	0.2647
Pooled	Incidence rate	60/260 (23.1%)	63/266 (23.7%)	73/259 (28.2%)
	comparison to sham: 2-sided p-value (Fisher-Test)	-	0.9181	0.1923

When pooling the two ranibizumab arms in both studies and comparing with sham, that is, 60/260 vs. 136/525, this difference is assessed by the 2-sided Fisher test to have a p-value of 0.4306.

Although three (instead of the expected two, under the assumption that there is no treatment effect) out of the four comparisons of the two trials revealed numerically higher incidence rates for ranibizumab as compared to sham, these differences were still in a range attributable to random effects and there was no consistency across the studies. While for BRAVO the numerically bigger difference to sham was seen for 0.3 mg (22.1% vs. 29.9%), in CRUISE the difference between these groups was reversed (24% vs. 17.4%), that is, in favour of ranibizumab.

Given the absence of both a statistical signal and consistency across studies, these data do not support a hypothesis of a safety concern under ranibizumab treatment regarding the fellow eye.

Evaluator Comment

The sponsor's response was acceptable. No further action was required. However, the incidence rate of AEs in the fellow eye was numerically higher in the ranibizumab 0.5 mg group than in the sham group in both BRAVO and CRUISE, although the differences were not statistically significant.

ii. In both studies, the most commonly occurring laboratory chemistry abnormality in the 12 month study period was elevated glucose levels in patients with normal baseline levels (14.0% to 23.7% of ranibizumab treated patients with glucose levels above the ULN). In the absence of a control group these results are difficult to interpret. In the

pooled data there were only 2 ranibizumab treated patients (0.4% [2/525]) with increased blood glucose reported as an AE in the 12 month study period. Increase blood glucose is not identified in the currently approved PI. However, the findings in the two pivotal RVO studies are of concern. Please comment on the findings of increased blood glucose levels in ranibizumab treated patients in the two pivotal RVO studies.

Sponsor Response

In the protocol and laboratory manual for BRAVO and CRUISE, patients were not required to fast before attending the visit during which samples were taken for evaluation of laboratory data, including blood glucose levels. This meant that there was a potential for a variation in blood glucose levels, based on the type and amount of food consumed prior to sampling. A variation in glucose levels was seen at both the screening and 12 month visits.

Therefore, for example, it can be seen that, in addition to 24% of the patients on 0.5 mg ranibizumab having high glucose levels at 12 months, there were 18% of patients on 0.5 mg ranibizumab with high glucose levels at baseline. This suggests that the abnormalities are due to variations in diet rather than an effect of Lucentis. In addition, medical history data show that, for the BRAVO and CRUISE studies pooled, 21.2% of the patients on sham/0.5 mg, 19.2% of patients on 0.3 mg ranibizumab and 20.8% of patients on 0.5 mg ranibizumab had diabetes mellitus.

There were four adverse events with the PT "blood glucose increased" reported, in total, from both studies. Two of the patients were in the sham/0.5 mg ranibizumab treatment group, one was on 0.3 mg ranibizumab and one was on 0.5 mg ranibizumab.

One of the four patients with an adverse event of "blood glucose increased" had a medical history of diabetes and one of the other patients had elevated glucose at screening. For the remaining two patients the increases in blood glucose were considered of mild severity by the reporting investigator, and all of these four adverse events were assessed as not suspected to be related to study medication.

In summary increased glucose blood levels were seen at Month 12 and at the baseline assessments and were most likely due to the non-fasting test conditions, as well as the fact that 20.4% of patients in these two studies had diabetes mellitus.

Evaluator Comment

The sponsor's response was acceptable. No further action was required.

iii. Increased ALT levels above the ULN in the 12 month study period were reported in both studies (~ 4% to 5% of patients with normal baseline levels) but no data on the degree of elevation above the upper level of normal could be identified in the submitted data. While hepatic toxicity does not appear to be a concern with ranibizumab, please comment on the findings of increased ALT levels in the two pivotal RVO studies. If available, please provide increased ALT levels grouped on the basis of the extent to which the ULN was increased (for example, 1.5 to 2.0 x ULN; 2 to 3 x ULN; > 3x ULN).

Sponsor Response

The mean change from baseline (and range) for ALT levels during the 12 month study period is shown for evaluable patients, by study, in Table 20.

Table 20: Changes from baseline in ALT levels, and patients with abnormal ALT levels, at Month 12 in BRAVO and CRUISE

	Sham/0.5 mg ranibizumab	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
BRAVO, evaluable patients (n)	98	113	121
Mean change from baseline (U/L)	-1.5	-1.1	-1.0
Range in change from baseline (U/L)	-37 to 25	-37 to 59	-71 to 45
Patients with normal baseline level and high ALT level at Month 12/ end of study (n)	9	4	5
CRUISE, evaluable patients (n)	102	120	109
Mean change from baseline (U/L)	-0.7	0.9	0.2
Range in change from baseline (U/L)	-32 to 37	-40 to 165	-53 to 40
Patients with normal baseline level and high ALT level at Month 12 / end of study (n)	8	6	5

Increases and decreases in ALT were seen between the baseline and Month 12/end of study evaluations. On average, however, there was a small decrease (approximately 1.0 U/L) in all treatment groups in the BRAVO study and less than 1.0 U/L change from baseline in all treatment groups in the CRUISE study.

Of the 18 patients in the BRAVO study who had ALT values within the normal range at baseline but above the ULN at the Month 12/end of study evaluation, the ALT value at Month 12/end of study was < 2 x ULN in 17 of the patients. The patient who had an increase from normal to > 2 x ULN was an 82 year old male patient with multiple co-morbidities, the most relevant of which were a history of jaundice, cholecystitis, kidney stones and gout (recent episodes), who had a baseline ALT of 21 U/L which increased to 80 U/L at Month 12 on 0.3 mg ranibizumab.

Of the 19 patients in the CRUISE study who had ALT values within the normal range at baseline but above the ULN at the Month 12/end of study evaluation, the ALT value at Month 12/end of study was < 59 U/L (< 2 x ULN) in 18 patients. In one patient in CRUISE there was an increase in ALT from 24 U/L at baseline to 189 U/L (> 3 x ULN) at Month 12 on 0.3 mg ranibizumab. This patient was a 39 year old male with no relevant medical history reported, but he drank > 14 units of alcohol per week. The increase in ALT was reported as a moderately severe adverse event of "elevated liver blood enzymes" (PT) which was not suspected by the reporting investigator to be related to ranibizumab.

Overall, there were no trends towards an increased average ALT value following 12 months of treatment with ranibizumab, and no indications of a dose effect. Only one patient of all the patients in both studies had an ALT which was > 3 x ULN and this patient had a reported high alcohol intake.

The overall changes in ALT levels from screening, with increases grouped on the basis of the extent to which the ULN was increased were provided.

Evaluator Comment

The sponsor's response was acceptable. No further action was required.

iv. Please comment on the increased uric acid levels reported in the two pivotal RVO studies.

Sponsor Response

The mean change from baseline (and range) for uric acid levels during the 12-month study period is shown for evaluable patients, by study, in Table 21.

Table 21: Changes from baseline in uric acid levels, and patients with abnormal uric acid levels, at Month 12 in BRAVO and CRUISE

	Sham/0.5 mg ranibizumab	Ranibizumab 0.3 mg	Ranibizumab 0.5 mg
BRAVO, evaluable patients (n)	100	114	122
Mean change from baseline (mg/dL)	0.12	-0.18	0.09
Range in change from baseline (mg/dL)	-5.9 to 3.2	-8.0 to 2.8	-2.7 to 2.9
Patients with normal baseline level and high uric acid level at Month 12 / end of study (n)[a]	6	4	8
CRUISE, evaluable patients (n)	102	121	110
Mean change from baseline (mg/dL)	0.04	0.03	0.28
Range in change from baseline (mg/dL)	-2.6 to 3.9	-2.3 to 3.3	-2.6 to 4.6
Patients with normal baseline level and high uric acid level at Month 12 / end of study (n)[a]	2	4	4

Both increases and decreases in uric acid were seen between the baseline and Month 12/end of study evaluations, as evidenced by the negative to positive range of values for the change from baseline. On average, however, the changes from baseline were very small (< 0.3 mg/dL).

Of the 18 patients in the BRAVO study who had uric acid values within the normal range at baseline but high at the Month 12/end of study evaluation, the uric acid value at Month 12/end of study was < 1.5 x ULN in all 18 patients.

Similarly, of the 10 patients in the CRUISE study who had uric acid values within the normal range at baseline and high at the Month 12/end of study evaluation, the uric acid value at Month 12/end of study was < 1.5 x ULN in all 10 patients.

Overall, there were no trends towards an increased average uric acid value following 12 months of treatment with ranibizumab, and no indication of a dose effect.

Evaluator Comment

The sponsor's response was acceptable. No further action was required.

v. Proteinuria was observed very commonly (> 10%) in ranibizumab treated patients in both studies and is an important potential risk of ranibizumab treatment identified in the RMP. In ***BRAVO***, among patients who had a negative result for urine protein at baseline, 11.5% of patients in the 0.3 mg group and 17.7% of patients in the 0.5 mg group had urine protein measured as either trace or 1 + in the last post-baseline urine sample. In ***CRUISE***, among patients who had a negative result for urine protein at baseline, 26.7% of patients in the 0.3 mg group and 12.8% of patients in the 0.5 mg group had urine protein measured as either trace or 1 + in the last post-baseline urine sample. However, no patients in the studies were reported as having proteinuria as an AE. Please comment on the relatively large number of patients in the two pivotal studies developing proteinuria with ranibizumab treatment.

Sponsor Response

In study BRAVO, there were 134 patients who received ranibizumab at a dose of 0.3 mg and 130 patients who received the 0.5 mg dose. Seventy five of the 85 patients (88.2%) on the 0.3 mg dose and 63 of the 77 patients (81.8%) at the 0.5 mg dose, who were negative for proteinuria at baseline were also negative at the Month 12/end of study visit. In CRUISE, there were 132 patients who received ranibizumab 0.3 mg and 129 patients who received 0.5 mg. Sixty two of the 84 patients (73.8%) on 0.3 mg and 68 of the 78 patients (87.2%) on 0.5 mg, who were negative for proteinuria at baseline were also negative at the Month 12/end of study visit.

The proportion of patients for whom urine protein was negative at baseline but had increased by the Month 12/end of study visit is shown in Table 22 (no patients had an increase from negative at screening to more than +1 at Month 12/end of study). Also shown is the proportion of patients whose urine protein decreased from trace or +1 at screening to negative at the Month 12/end of study visit.

Table 22: Increased urine protein levels in patients in the BRAVO and CRUISE studies

	Number of patients (%)					
	BRAVO		CRUISE		POOLED DATA	
	0.3 mg (134)	0.5 mg (130)	0.3 mg (132)	0.5 mg (129)	0.3 mg (266)	0.5 mg (259)
Negative urine protein at screening, trace at Month 12 / end of study (↑)	5 (3.7)	11 (8.5)	16 (12.1)	9 (7.0)	21 (7.0)	20 (7.7)
Negative urine protein at screening,+1 at Month 12 / end of study (↑)	5 (3.7)	3 (2.3)	6 (4.5)	1 (0.8)	11 (4.1)	4 (1.5)
Trace urine protein at screening, negative at Month 12 / end of study (↓)	6 (4.5)	9 (6.9)	5 (3.8)	11 (8.5)	11 (4.1)	20 (7.7)
+1 urine protein at screening, negative at Month 12 / end of study (↓)	0 (-)	2 (1.5)	8 (6.1)	1 (0.8)	8 (3.0)	3 (1.2)

In both studies, of those patients who demonstrated an increase from negative protein in the urine to positive, all were either “trace” or “+1” at Month 12/end of study. Additionally, some patients who had proteinuria at baseline had reductions in the urine protein level at study end. For example, in addition to 9.2% of patients on 0.5 mg ranibizumab having negative proteinuria at screening and trace or +1 protein in the urine at Month 12/end of study, there were 8.9% of patients on 0.5 mg ranibizumab with trace or +1 protein in the urine at screening who were negative at Month 12/end of study. A similar situation was seen on 0.3 mg ranibizumab, where 11.1% of the patients had negative proteinuria at screening and trace or +1 protein in the urine at Month 12/end of study, and 7.1% of patients had trace or +1 protein in the urine baseline and were negative at Month 12/end of study.

There were a total of two adverse events of proteinuria, both reported in BRAVO. In both studies, laboratory abnormalities that result in study withdrawal, meet serious criteria, are associated with clinical signs or symptoms, or require medical intervention were recorded as AEs or SAEs. Therefore these were the only two increases in urine protein that were considered by the investigator to have met those criteria. One was a report of a 67 year old female patient with a history of hypertension on 0.3 mg ranibizumab who had a negative urine protein and microscopy at screening which became positive at Month 12 (urine hyaline cast of 4 and trace protein). The event was assessed as moderately severe and not suspected to be related to treatment. The second report described a 65 year old

male patient with diabetes and a history of kidney stones on 0.5 mg ranibizumab. The patient had trace urine protein at both screening and Month 12. The AE was assessed as mild in severity and was not suspected to be related to ranibizumab but due to underlying illness. This patient also had AEs of frequent urination, haematuria and kidney stones reported during the study.

Finally, many patients in both studies had hypertension, diabetes or other underlying conditions (that is, urinary tract infection, renal disorders) which could have predisposed them to protein in the urine. When used systemically, anti-VEGF agents may plausibly contribute to proteinuria, since VEGF is involved in the control of vascular tone and glomerular capillary function. The systemic exposure to IVT Lucentis is very small. Nonetheless, proteinuria will continue to be closely monitored and is an important identified risk in the current Lucentis Risk Management Plan (RMP).

Evaluator Comment

The sponsor's response was acceptable. Proteinuria in patients treated with IVT ranibizumab appears to be due to a systemic pharmacological effect of the drug on renal circulation and glomerular function. The sponsor stated that it will continue to closely monitor proteinuria. It was noted that proteinuria is an important identified risk in the RMP. It was recommended that the sponsor continues to report specifically on cases of proteinuria in the Periodic Safety Update Reports (PSURs) for Lucentis.

vi. The safety data for the two pivotal studies included AEs grouped under the term "hypersensitivity" reflecting the concerns discussed in the RMP relating to the important identified risk of "hypersensitivity reactions". Please provide a breakdown of "hypersensitivity" AEs occurring in both pivotal studies by individual preferred terms contributing to this event.

Sponsor Response

The sponsor provided tables shown by PT of the AEs in the RMP risk 'Hypersensitivity' which were reported in the pooled BRAVO and CRUISE studies.

Evaluator Comment

The "hypersensitivity" data in patients treated with ranibizumab 0.5 mg do not give rise to significant safety concerns. The preferred term events in the RMP risk category "hypersensitivity" in the pooled data from BRAVO and CRUISE in patients treated for up to 6 months with sham or ranibizumab 0.5 mg are summarised Table 23. The reactions include ocular and non-ocular adverse events. There were no marked differences in the incidence rate between the sham treated group and the ranibizumab 0.5 mg treated group. The most commonly reported events (≥ 1.0% in either group) were (sham vs ranibizumab 0.5 mg): eye pruritus (3.1% vs 1.2%); eyelid oedema (1.5% vs 0.8%); drug hypersensitivity (1.2% vs 0.4%); and rash (1.2% vs 0.8%).

Table 23: Number of patients with RMP risk category Hypersensitivity by Preferred Term: pooled studies Bravo and Cruise patients treated for up to 6 months safety population

Preferred Term	Sham (N=260) n (%)	Lucentis 0.5 mg (N=259) n (%)
ANGIOEDEMA	1(0.4)	0(0.0)
CONJUNCTIVAL OEDEMA	0(0.0)	2(0.8)
CONJUNCTIVITIS ALLERGIC	1(0.4)	0(0.0)
DERMATITIS CONTACT	0(0.0)	2(0.8)
DRUG HYPERSENSITIVITY	3(1.2)	1(0.4)
ERYTHEMA OF EYELID	1(0.4)	0(0.0)
EYE ALLERGY	0(0.0)	1(0.4)
EYE PRURITUS	8(3.1)	3(1.2)
EYE SWELLING	0(0.0)	1(0.4)
EYELID OEDEMA	4(1.5)	2(0.8)
EYELIDS PRURITUS	1(0.4)	0(0.0)
HYPERSENSITIVITY	1(0.4)	3(1.2)
PERIORBITAL OEDEMA	1(0.4)	0(0.0)
RASH	3(1.2)	2(0.8)

Multiple occurrences of the same event in a patient were counted only once.

In the pooled BRAVO and CRUISE data for the ranibizumab 0.5 mg dose in patients treated for up to 1 year in the safety population (n=259) the incidence rates of RMP risk category "hypersensitivity" preferred terms were: hypersensitivity 2.3% (n=6); eye pruritus 1.9% (n=5); rash 1.5% (n=4); conjunctival haemorrhage 1.2% (n=3); drug hypersensitivity 1.2% (n=3); dermatitis contact 0.8% (n=2); eyelid oedema 0.8% (n=2); conjunctivitis allergic 0.4% (n=1); eye allergy 0.4% (n=1); and eye swelling 0.4% (n=1). The preferred terms included ocular and non-ocular adverse events. There was no evidence that increasing the duration of exposure from 6 months to 1 year increased the incidence of hypersensitivity reactions.

vii. The safety data for the two pivotal studies included AEs grouped under the term "intraocular inflammation" reflecting the concerns discussed in the RMP relating to the important identified risk of these reactions. Please provide a breakdown of "intraocular inflammation" AEs occurring in both pivotal studies by the individual preferred terms contributing to this event.

Sponsor Response

The sponsor provided tables shown by PT of the AEs in the RMP risk 'Intraocular inflammation'.

Evaluator Comment

The "intraocular inflammation" in the study eye data in patients treated with ranibizumab 0.5 mg do not give rise to significant safety concerns. There were no marked differences in the incidence rate between the sham treated group and the ranibizumab 0.5 mg treated group, and 4 out of the 5 events occurred more frequently in the sham group than in the ranibizumab group.

In the pooled BRAVO and CRUISE data for the ranibizumab 0.5 mg dose in patients treated for up to 1 year in the safety population (n=259), the incidence rates of the RMP risk "intraocular inflammation" by preferred term were: macular oedema 10.4% (n=27); ocular hyperaemia 7.3% (n=19); iritis 0.8% (n=2); and retinal oedema 0.4% (n=1). The adverse events of macular oedema and ocular hyperaemia occurred more frequently in patients in the ranibizumab 0.5 mg treated for up to 1 year than for up to 6 months.

viii. Please account for the differences in the number of non-ocular AEs for certain events described by the same term reported in the same population in the general summary of AEs compared with the summary of AEs reflecting RMP safety concerns.

Sponsor Response

The sponsor provided a satisfactory answer to this discrepancy

Evaluator Comment

The sponsor's response was acceptable. No further action was required.

PI and CMI

There were a number of questions relating to the proposed PI and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

Risk Management Plan

There were also a number of questions raised concerning the Risk Management Plan (RMP)(*Section V*). These are discussed in that section.

Clinical Summary and Conclusions

Assessment of benefits

Both doses of ranibizumab (0.3 mg and 0.5 mg) produced clinically meaningful improvements in visual acuity (BCVA), retinal anatomy (central foveal thickness) and self reported visual function (near and distance activities) at 6 months compared with sham treatment in patients with impaired VA due to macular oedema secondary to BRVO or CRVO. These clinical improvements were observed with IVT injections in the study eye at monthly intervals for a total or 6 injections. Improvement in visual acuity and retinal anatomy were observed as early as 7 days after the first ranibizumab injection and continued to improve through to Month 6, and were then maintained through to Month 12 with ranibizumab being administered monthly on an "as needed" basis. There were no data in the submission on maintenance of efficacy beyond 12 months.

Neither of the two pivotal studies included statistical analyses of the efficacy outcomes comparing the two ranibizumab doses. In general the higher dose resulted in increased efficacy but the differences in efficacy outcomes between the two doses were small. However, it is considered that the efficacy data support the approval of the 0.5 mg dose rather than the 0.3 mg as, on average, more patients are likely to benefit from the higher dose than the lower dose and the safety profiles of the two doses do not significantly differ. The availability of ranibizumab 0.5 mg will provide an additional approved treatment option to laser therapy alone for Australian patients with BRVO, and an approved treatment for Australian patients with CRVO where non currently exist.

In both pivotal studies, treatment with ranibizumab statistically significantly ($p< 0.0001$) increased mean BCVA from baseline compared with sham at Month 6 (primary efficacy endpoint). In ***BRAVO***, the increase in mean BCVA from baseline at month 6 was 16.6 letters in the 0.3 mg group (n=134) and 18.3 letters in the 0.5 mg group (n=131) compared with 7.3 letters in the sham group (n=132). In ***CRUISE***, the increase in mean BCVA from baseline at Month 6 was 12.7 letters in the 0.3 mg group (n=132) and 14.9 letters (n=130) in the 0.5 mg group compared with 0.8 letters in the sham group (n=130). In both studies, it was considered that the increased BCVA observed with ranibizumab is clinically meaningful.

In both pivotal studies, analyses of the secondary efficacy endpoints consistently supported the analyses of the primary efficacy endpoint. In particular, the proportion of patients gaining ≥ 15 letters from baseline at Month 6 and the proportion of patients with central foveal thickness ≤ 250 μm at Month 6 were statistically significantly greater in both ranibizumab dose groups compared with sham in both studies. Furthermore, these observed differences are considered to be clinically significant. Overall, the number

needed to treat (NNT) with ranibizumab to gain ≥ 15 letters at Month 6 from baseline was about 3 to 4 patients, and the NNT to achieve central foveal thicknesses of ≤ 250 µm at Month 6 was about 2 to 3 patients. Self reported improvement in visual function at 6 months as assessed by NEI VFQ-F25 subscales for near and distance activities were also statistically significant for both doses of ranibizumab compared with sham in both studies.

The 6 month observation period data showed that the clinical benefits achieved after the initial 6 monthly injections of ranibizumab can be maintained for a further 6 months with a follow up regimen involving monthly ranibizumab injections administered on an "as needed" basis. The re-treatment criteria in the treated eye were a BCVA of 20/40 or worse (Snellen equivalent) using ETDRS charts or a mean central subfield thickness ≥ 250 µm on OCT. In ***BRAVO*****,** the average number of ranibizumab "as needed" injections per patient in the 6 month observational period was higher in the sham/0.5 mg treatment group than in both the 0.3 mg and 0.5 mg groups (3.6, 2.8 and 2.7 injections, respectively). In ***CRUISE***, the average number of ranibizumab "as needed" injections received per patient in the 6 month observation period was similar in the sham/0.5mg, 0.3 mg and 0.5 mg treatment groups (3.7, 3.8 and 3.3 injections, respectively). In the two studies, the percentage of all randomized patients re-treated with ranibizumab during the observation period at Month 6 (first opportunity for re-treatment) was (BRAVO; CRUISE, respectively): 78.8%; 76.9% in the sham/0.5 mg group; 41.0%; 56.1% in the 0.3 mg group; and 38.2%; 49.2% in the 0.5 mg group. During the 6 month observation period, the percentage of patients treated with ranibizumab "as needed" was (BRAVO; CRUISE, respectively): 87.1%; 84.6% in the sham/0.5 mg group; 79.1%; 90.9% in the 0.3 mg group; and 76.3%; 84.4% in the 0.5 mg group.

In ***BRAVO***, at Month 12 the mean change from baseline in BCVA score (vs Month 6) for the sham/0.5 mg, 0.3 mg and 0.5 mg groups was 12.1 (vs 7.3) letters, 16.4 (vs 16.6) letters, and 18.3 (vs 18.3) letters, respectively. In ***CRUISE***, the corresponding results were 7.3 (vs 0.8) letters, 13.9 (vs 12.7) letters, and 13.9 (vs 14.9 letters). In ***BRAVO***, at Month 12 the proportion of subjects gaining ≥ 15 letters in VA score from baseline (vs Month 6) for the sham/0.5 mg, 0.3 mg and 0.5 mg groups was 43.9% (28.8%), 56.0% (vs 55.3%) and 60.3% (vs 61.1%), respectively. In ***CRUISE***, the corresponding results were 33.1% (vs 16.9%), 47.0% (vs 46.2%) and 50.8% (vs 47.7%). In ***BRAVO***, at Month 12 the proportion of subjects with central foveal thickness of ≤ 250 µm (vs Month 6) for the sham/0.5 mg, 0.3 mg and 0.5 mg groups was 78.8% (45.5%), 83.6% (vs 91.0%) and 86.3% (84.7%), respectively. In ***CRUISE***, the corresponding results were 70.8% (23.1%), 75.8% (vs 75.0%) and 77.7% (vs 76.9%).

There were no data in patients with BRVO comparing laser therapy with ranibizumab and laser therapy has been considered to be standard treatment for this condition for about the last 20 to 25 years. In ***BRAVO*****,** laser rescue treatment was administered to 27 (20.1%) patients in the ranibizumab 0.3 mg group, 28 (21.4%) in the ranibizumab 0.5 mg group and 76 (57.6%) in the sham group during the 6month treatment period (beginning at Month 3). At least one laser treatment during the total 12 month treatment period was received by 81 (61.4%), 55 (41.0%) and 45 (34.4%) patients in the sham, ranibizumab 0.3 mg and ranibizumab 0.5 mg treatment groups, respectively, indicating that laser treatment was commonly used in addition to ranibizumab in patients with BRVO. However, at Month 3 of the 6 month treatment period (after the third injection and before laser therapy) the mean (SD) increase in BCVA from baseline was 4.5 (12.5), 13.0 (9.6) and 15.3 (11.8) letters for the sham, 0.3 mg and 0.5 mg groups, respectively, with the difference between 0.3 mg and sham being 8.5 letters ([95%CI: 5.8. 11.1]; p< 0.0001) and between 0.5 mg and sham being 10.8 letters ([95%CI: 7.8, 13.8]; p< 0.0001). Consequently, the lower rates of laser reuse treatment in the ranibizumab groups compared with the sham group in the 6 month treatment period and the clinically and statistically significantly greater increases

in VA at Month 3 after the third injection and before laser rescue treatment in both the ranibizumab groups compared with the sham group strongly suggest that ranibizumab treatment has a beneficial effect on BRVO unrelated to laser therapy.

The efficacy over time data in ***BRAVO*** and ***RESOLVE*** and the exploratory analyses in the submission relating to maintenance of stability and retreatment support the proposed dosing regimen. However, the proposed treatment regimen differs from that in the two pivotal studies in which the protocols specified that all patients had treatment initiated with 6 injections administered at monthly intervals in the 6 month treatment period with further treatment being determined by maintenance of response criteria. In the proposed regimen it is possible that some patients will have treatment discontinued due to stability being achieved as early as the third month after initiation of treatment (after the third monthly injection). It was considered that the proposed treatment regimen should include an option for stopping treatment if no improvement has been observed after the third initial injection. Treatment decisions in individual patients relating to discontinuation for VA stability and retreatment for loss of VA stability will rest with individual clinicians as no specific VA letter criteria relating to treatment decisions have been specified in the PI.

Assessment of risks

The safety profile of ranibizumab for the treatment of visual impairment due to macular oedema secondary to RVO is similar to that for the treatment of wet-AMD. No significant new safety signals emerged from the data. Overall, the safety profiles of the 0.3 mg dose and the 0.5 mg dose were similar and there were no clinically meaningful increased risks associated with the high dose compared with the low dose. The cumulative 12 month safety profiles of the 0.3 mg and 0.5 mg groups were consistent with those observed at 6 months. There were 5 deaths in the two pivotal studies and 2 deaths in the extension study. One of the deaths in ***BRAVO*** (respiratory failure preceded by cerebral haemorrhage in a 78 year old male) was considered by the investigator to be related to the study drug. The risks discussed below relate to the pooled data from the safety evaluable population in both pivotal studies, unless otherwise stated.

There were no safety data in patients with RVO treated with ranibizumab for longer than 12 months and this is a deficiency in the submission. In addition, there was no control group (sham treatment only) in the 6 month observation period of the pivotal studies. Consequently, the safety data in the 6 month observational data relating to ranibizumab is not sham controlled. The sham group in the 6 month treatment group were eligible for treatment with ranibizumab 0.5 mg in the 6 month observational period and about 85% of patients in the sham groups were treated with ranibizumab in this period. However, despite the limitations of the safety data it is considered that the submitted data have satisfactorily established the safety of ranibizumab for the proposed indication.

The risk of experiencing at least one ocular AE in the study eye was high in the pivotal studies in patients in both the combined ranibizumab group (6 and 12 month data) and the sham group (6 month data). In the 6 month treatment period, ocular AEs in the study eye were reported more frequently in patients in the ranibizumab 0.3 mg (80.8% [215/266]) and 0.5 mg (81.1% [210/259]) groups than in the sham group (76.9% [200/260]). In both ranibizumab groups about 4% to 5% more patients experienced at least one ocular AE than sham treated patients (NNT 20 to 25 patients). However, the increased risk of ocular AEs with IVT injections of ranibizumab compared with sham non-penetrative injections is not unexpected. In the 12 month study period, ocular AEs in the study eye were reported in 90.2% (n=240) and 88.4% (n=229) of patients in the ranibizumab 0.3 and 0.5 mg treatment groups, respectively.

The most frequently reported ocular AE in the study eye in the 6 month treatment period was conjunctival haemorrhage, reported in 49.7% of patients in the combined ranibizumab group and 37.3% of patients in the sham group. Other ocular AEs in the study eye occurring in ≥ 5% of patients in the combined ranibizumab group and more frequently than in the sham group in the 60 month treatment period were retinal exudates (23.4% vs 12.7%), eye pain (17.0% vs 12.3%), maculopathy (12.2% vs 7.3%), retinal vascular disorder (11.8% vs 9.2%), retinal haemorrhage (11.6% vs 11.2%), maculopathy (12.2% vs 7.3%), myodesopsia (8.4% vs 2.3%), retinal depigmentation (7.6% vs 4.2%), foreign body sensation in the eye (7.2% vs 5.0%), increased intraocular pressure (6.7% vs 2.3%), ocular vascular disorder (6.5% vs 5.0%) and ocular hyperaemia (5.9% vs 2.7%). Most ocular AEs in the study eye occurring in the 6 month treatment period were categorized by investigators as non-severe, with ocular severe AEs occurring more commonly in the sham group (3.8%) than in the combined ranibizumab group (2.7%).

Ocular SAEs in the study eye in the 6 month treatment period were infrequent and were reported in 3.1% of patients in the sham group and 2.1% of patients in the combined ranibizumab group. Discontinuations due to ocular AEs in the study eye in the 6 month treatment period were also infrequent and were reported in 1.9% of patients in the sham group and 0.4% of patients in the combined ranibizumab group.

In the 12 month study period, ocular AEs in the study eye occurring in ≥ 10% of patients in the combined ranibizumab group (n=525) were conjunctival haemorrhage (52.2%), retinal exudates (29.0%), retinal haemorrhage (25.0%), maculopathy (21.3%), retinal vascular disorder (20.6%), eye pain (19.6%), macular oedema (11.8%), retinal depigmentation (10.7%) and myodesopsia (10.7%). Most ocular AEs occurring in the 12 month treatment period were categorized by investigators as non-severe and ocular severe AEs occurred in only 3.6% of patients in the combined ranibizumab group.

Ocular AEs in the study eye of special interest noted in the RMP and considered to reflect important identified and potential risks with ranibizumab treatment are deterioration of retinal blood flow, intraocular inflammation, increased intraocular haemorrhage, vitreous haemorrhage, traumatic cataract, retinal tear, retinal detachment and endophthalmitis. The risk of patients experiencing at least one of these key ocular AEs in the 6 month treatment period was identical in the sham and combined ranibizumab groups (31.2% [n=81] vs 31.2% [n=164], respectively). Key ocular AEs occurring more frequently in patients in the combined ranibizumab group than in the sham group were raised intraocular pressure (7.0% vs 3.8%), retinal tear (0.6% vs 0%) and endophthalmitis (0.2% vs 0%). In the 12 month study period, the risk of patients experiencing at least one of these key ocular AEs was 51.8% in the combined ranibizumab group and events occurring in ≥ 10% of patients were deterioration of retinal blood flow (25.5%), intraocular inflammation (20.2%) and increased intraocular pressure (12.0%).

The risk of experiencing a non-ocular AE in the 6 month treatment period was similar in the combined ranibizumab group (52.8% [n=277]) and the sham group (51.5% [n=134]). The only non-ocular AEs reported in ≥ 5% of patients in the combined ranibizumab group (vs sham) were hypertension (5.5% vs 8.1%) and nasopharyngitis (5.3% vs 3.8%). In the 12 month study period, 70.1% (n=368) of patients in the combined ranibizumab group experienced at least one non-ocular AE, and events occurring in ≥ 5% of patients were hypertension (9.9%), nasopharyngitis (7.6%) and sinusitis (6.7%).

Non-ocular SAEs in the 6 month treatment period were reported more frequently in the combined ranibizumab group (8.8%) than in the sham group (5.8%). However, in neither treatment group were individual AEs reported in more than 2 patients. The individual non-ocular SAEs of special interest reported in 2 patients in the combined ranibizumab group but less than 2 patients in the sham group were hypertension (2 [0.4% vs 1 [0.4%])

and MI (2 [0.4%] vs 0 [0%]). In the 12 month study period, non-ocular SAEs were reported in 13.1% (n=69) of patients in the ranibizumab group and the only event to occur in ≥ 1% of patients was pneumonia (1.0%).

Non-ocular AEs resulting in discontinuing in the 6 month treatment period were uncommon and occurred in 1.0% (n=5) of patients in the combined ranibizumab group and 0.8% (n=2) of patients in the sham group. Of the 5 non-ocular AEs resulting in discontinuations in the 5 patients in the combined ranibizumab group, 3 were related to cardiovascular disease (MI, arteriosclerosis coronary artery, cerebral haemorrhage), compared with none of the 2 events in the 2 patients in the sham group. In the 12 month study period, non-ocular AEs resulting in discontinuation occurred in 1.1% (n=6) patients in the combined ranibizumab group and 4 of the 7 reported individual events in the 6 patients were cardiovascular in origin.

Systemic AEs of special interest noted in the RMP and considered to reflect important identified and potential risks with ranibizumab treatment are hypersensitivity, hypertension, non-ocular haemorrhage, proteinuria, MI, other arterial thromboembolic events and venous thromboembolic events. The risk of patients experiencing at least one of these key systemic AEs in the 6 month treatment period was greater in the sham group (20.8% [n=54]) than in the combined ranibizumab group (17.1% [n=90]). The only 2 key systemic AEs reported in ≥ 5% of patients in both the combined ranibizumab and sham groups in the 6 month treatment period were hypersensitivity (8.2% vs 8.1%, respectively) and hypertension (6.7% vs 10.0%). Of the other key systemic AEs events reported in the 6 month treatment period, the only 2 reported more frequently in the combined ranibizumab group than in the sham group were MI (0.6% vs 0.4%) and other arterial events (1.3% vs 0.8%). In the 12 month study period, key systemic AEs occurred in 25.3% (n=133) of patients in the combined ranibizumab group, with events occurring in ≥ 2% of patients being hypertension (12.0%), hypersensitivity (10.5%) and other arterial thromboembolic events (2.1%).

APTC arterial thromboembolic events were investigated in both pivotal studies (vascular deaths, non-fatal MIs, non-fatal ischaemic CVAs and non-fatal haemorrhagic CVAs). In the 6 month treatment period, the risk of patients experiencing at least one of these arterial thromboembolic events were identical in the combined ranibizumab (0.8% [n=4]) and sham (0.8% [n=2]) groups. The individual events in the 4 patients in the ranibizumab group were 3 non-fatal MIs and 1 fatal haemorrhagic CVA, and in the 2 patients in the sham group were 1 non-fatal MI and 1 non-fatal haemorrhagic CVA. In the 12 month treatment period, there were 6 (1.1%) patients in the combined ranibizumab group who experienced an arterial thromboembolic event (2 x MI, 2 x CVA, 1 x embolic stroke, 1 x death due to unknown cause).

Overall, in ***BRAVO*** in the 6 month treatment period, AEs (any) potentially related to systemic VEGF inhibition occurred more commonly in the sham group than in the 0.3 mg and 0.5 mg groups (14.5% [18/131], 11.2% [15/134] and 11.5% [15/130], respectively). Review of these AEs shows that the events reported more frequently in the combined ranibizumab group than in the sham group were myocardial infarction (0.4% [n=1] vs 0), unstable angina (0.4% [n=1] vs 0), cerebral haemorrhage (0.4% [n=1]), retinal artery embolism (0.4% [n=1] vs 0), intra-abdominal haematoma (0.4% [n=1] vs 0), post procedural haemorrhage (0.4% [n=1] vs 0), rectal haemorrhage (0.4% [n=1] vs 0) and intestinal perforation (0.4% [n=1] vs 0). In the 12 month study period, AEs (any) potentially related to systemic VEGF inhibition occurred in 18.6% (49/264) of patients in the combined ranibizumab group and the only 2 events occurring in ≥ 2% of patients were increased blood pressure (3.0% [n=9]) and hypertension (12.5% [n=33]).

Overall, in ***CRUISE*** in the 6 month treatment period, AEs (any) potentially related to systemic VEGF inhibition occurred more commonly in the sham group than in the 0.3 mg and 0.5 mg groups (10.1% [n=13], 6.8% [n=9] and 7.0% [n=9], respectively). Review of these AEs shows that the events reported more frequently in the combined ranibizumab group than in the sham group were MI (0.8% [n=2] vs 0), retinal artery embolism (0.4% [n=1] vs 0), retinal artery occlusion (0.4% [n=1] vs 0), retinal infarction (0.4% [n=1] vs 0), transient ischaemic attack (2 [0.8%] vs 0), haematoma (0.4% [n=1] vs 0) and periorbital haematoma (0.4% [n=1] vs 0). In the 12 month study period, AEs (any) potentially related to systemic VEGF inhibition occurred in 14.6% (38/261) of patients in the combined ranibizumab group and the only event occurring in ≥ 2% of patients was hypertension (7.3% [n=19]).

Laboratory tests abnormalities giving rise to potential safety signals in ranibizumab treated patients were uncommon. The observed laboratory test abnormalities of concern were: reductions in haematocrit, haemoglobin levels and red blood cell counts; increased glucose levels; increased ALT levels; increased uric acid levels; and proteinuria. However, AE events related to these laboratory abnormalities were reported infrequently and anaemia is a recognized AE that has been previously reported with ranibizumab.

The seroconversion rate in ranibizumab treated patients was small (2.0% [9/444]). Although the sponsor concluded that there were no relevant differences in AEs between antibody positive and antibody negative patients, it was considered that the number of antibody positive patients was too small to allow clinically meaningful comparisons between the two patient groups to be made.

Overall, there were no particular additional safety concerns associated with ranibizumab treatment in special groups and situations (intrinsic and extrinsic) as assessed by those AEs reflecting the identified and potential safety concerns in the RMP.

Assessment of benefit risk balance

The benefit risk balance of ranibizumab for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion is favourable for the proposed 0.5 mg dose.

Recommendation Regarding Authorisation

It was recommended that the submission to extend the indications of Lucentis (ranibizumab) for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO) should be approved.

It was also recommended that the provision of the final Clinical Study Reports for studies FVF3426g and RFB002A2406 should be a condition of registration. These reports should be submitted to the TGA for evaluation as soon as practical after completion.

V. Pharmacovigilance Findings

Risk Management Plan

Safety Specification

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR). The summary of the Ongoing Safety Concerns as specified by the sponsor is shown in Table 24.

Table 24: Ongoing safety concerns for Lucentis

Important identified risks	
	Hypersensitivity reactions
	Retinal pigment epithelial tear
	Endophthalmitis
	Retinal detachment
	Retinal tear
	Traumatic cataract
	Intraocular inflammation
	Intraocular pressure increase
	Vitreous hemorrhage
Important potential risks	
	Hypertension
	Non-ocular hemorrhage
	Proteinuria
	Myocardial infarction
	Non-MI Arterial thromboembolic events
	Venous thromboembolic events
	Deterioration of retinal blood flow including CRAO
Important missing information	
	Systemic adverse events related to bilateral treatment and overdose
	Adverse events related to off-label use, including potential local and systemic adverse events related to pediatric off-label use (e.g. retinopathy of prematurity)
	Long-term safety beyond two years
	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 only)
	Effects of Lucentis on the deterioration of retinal blood flow including macular ischemia (DME only)
	Systemically unstable patients (DME only)
	Age greater than 75 years (DME only)
	Ethnicities other than Caucasian (DME only)

The clinical aspects of the safety specification in the draft RMP were reviewed by the clinical evaluator and were considered satisfactory. The OPR reviewer noted that the safety specification was acceptable.

Pharmacovigilance Plan

For all ocular safety concerns, routine pharmacovigilance will be supported by the targeted follow up of all serious postmarketing and clinical trial reported adverse events using a questionnaire/checklist.[16] These questionnaires collect further information on the description of the event and patient history details.

One planned (LUMINOUS) and three ongoing studies are proposed to address all identified and potential risks, both ocular and non-ocular. LUMINOUS is proposed as a long term observational study to observe the effectiveness and safety of Lucentis through individualized patient treatment and associated outcomes.

Ongoing studies include the prospective cohort study, Epi-COHORT in wet-AMD, the long term extension study SECURE in wet-AMD) (CRFB002A2402) and the long term extension of RESTORE study in visual impairment due to DME.

Some of the above studies are also proposed to inform some of the non-ocular missing information safety concerns, specifically:

- Systemic adverse events (bilateral treatment and overdose) – cohort (Epi-COHORT) study
- Long term safety beyond 2 years – SECURE, RESTORE and LUMINOUS
- Long term effects on progression of diabetic retinopathy and effects of Lucentis on the deterioration of retinal blood flow including macular ischaemic – RESTORE
- Systemically unstable patients

The OPR reviewer noted that the protocols of the ongoing studies have not been reviewed as these are already in progress, however the following comments were provided. The LUMINOUS protocol has been reviewed.

The Epi-COHORT, SECURE and RESTORE studies are conducted in different population groups (wet-AMD and DME) and therefore generalisability of the results will need to be considered. The patient years of follow up (approx 1540, 693, 1170 respectively) for these studies also may reveal very few adverse event reports given the postmarketing cumulative reporting rates so far are <1/1,000 patient years.

The clinical evaluator confirmed the lack of safety information beyond 12 months as a current deficiency that should be addressed. In the RMP the sponsor identified the LUMINOUS study and the SECURE and RESTORE extension studies, as additional pharmacovigilance activities for this concern. The extension studies involve a total follow up period of 3 years and LUMINOUS for 5 years. Only the LUMINOUS study will contain patients with macular oedema secondary to RVO. However, the clinical evaluation report identifies an extension study (HORIZON, FVF3426g) which is completed but the Clinical Study Report was not provided as part of the submission, which will provide data on the "long term persistence of treatment effect (up to 24 months)". No comment could be made on the contribution of this extension study, as it is not included in the RMP.

[16] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The targeted follow up of ocular events will allow for more detailed information to be collected including a description of the event and the patient history. This is appropriate, and will contribute to reducing the impact of missing information as well.

Risk Minimisation Activities

The sponsor proposed that routine risk minimisation activities are adequate for safety concerns apart from endophthalmitis and traumatic cataract.[17]

The OPR reviewer noted that an elevated relative risk has been identified with both endophthalmitis and traumatic cataract in the clinical study program. In addition post marketing experience identifies endophthalmitis as having one of the highest cumulative reporting rates (0.31 per 1,000 patient years). The mechanism of action proposed for both these risks is a complication of IVT injection and therefore it was suitable that additional activities be considered for these two risks.

For the remaining ocular concerns, there is also a potentially elevated relative risk for intraocular pressure (IOP) increase. In their analysis, the sponsor identifies that the majority of IOP events in DME were from the study (RESOLVE) in which a volume of 100 µL ranibizumab was given to the majority of patients (22 of the 24 reports). In a further study (RESTORE) the indicated dose and volume (0.5 mg in 50 µL) was used in all patients and only 2 reports were received. This reduction in injected volume has appeared to reduce the risk of IOP events.

Another ocular safety concern with a similar cumulative reporting rate to endophthalmitis is intraocular inflammation. This may arise as a complication of IVT injection or in the presence of a history of intraocular infection or inflammation. The additional activities for endophthalmitis and traumatic cataract will also address the risk of intraocular inflammation, as does the information in the PI. For completeness however, it would be appropriate to include this safety concern as being addressed by additional risk minimisation activities in the next RMP update.

For the non-ocular safety concerns, the theoretical mechanism of action is related to the systemic effects of anti-VEGF, and there is no statistically significant elevated risk at this stage. Post marketing experience reports a cumulative reporting rate of 0.33 for hypersensitivity reactions and 0.34 for non-MI arterial thromboembolic events, while the remainder are all less than 0.1 per 1,000 patient years. Routine risk minimisation was considered acceptable for these concerns.

The additional risk minimisation activities for endophthalmitis and traumatic cataract are a healthcare professional and patient educational plan. The objectives of these activities are:

- To prevent or minimise the likelihood of IVT injection related adverse events, and
- To inform and educate physicians and patients on early recognition and management of these events.

These educational plans were developed to address potential IVT injection procedure related safety risks as part of risk management for the current indication of wet-AMD. The development of the professional and patient educational material for the indication of wet-AMD appear to have been well constructed in Europe and the translation for the Australian context has involved good consultation with appropriate specialists and patients. There also appears to be effective mechanisms for receiving and incorporating feedback from both health care professionals and patients into further revisions of these

[17] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

materials. The development of updated materials to reflect the new indication will include a similar consultation process, and ongoing feedback mechanisms. It was also acknowledged that the prescribers and users of IVT ranibizumab under this extended indication will be very similar, if not the same, as the current users.

Pharmacovigilance Summary and Conclusions

The safety specifications were acceptable.

The lack of longer term safety information is identified in the RMP as 'missing information' and supported by the clinical evaluator. The following comments were provided to the delegate on how this is addressed:

- The clinical evaluation report identifies an extension study (HORIZON, FVF3426g) which is completed but the clinical study report was not provided as part of the submission, which will provide data on the "long term persistence of treatment effect (up to 24 months)". This is not included in the RMP, and as such no comment can be provided on this, however it is assumed it will provide information relevant to this new indication.
- The RMP identifies 3 studies, the LUMINOUS study (5 year duration), and the SECURE and RESTORE extension studies (total follow up period of 3 years), as addressing this ongoing safety concern in general. None of these studies are focused on the RVO population, however the LUMINOUS study will include patients across all indications.
- The PV activities in the RMP will not provide additional long term safety information specific to the current requested indication (RVO). Whether further activities are required for this indication will depend on the details of the extension study (HORIZON, FVF3426g).

Otherwise, the pharmacovigilance plan was acceptable.

The Risk Minimisation Plan was acceptable.

There was also a recommendation concerning the PI but that is beyond the scope of this AusPAR

List of Questions

(i) The LUMINOUS study is planned as an additional PV activity to address many of the important identified and potential risks, and some of the missing information safety concerns. Annex 5, titled "Protocols of proposed and ongoing studies in pharmacovigilance plan" contains a list of these studies but not the protocol itself. The RMP document contains some information, but not enough to assess the ability of the study to address the safety concerns, including important study design features such as power/sample size, bias and confounding. Please provide the current version of the LUMINOUS study protocol.

Sponsor response

The sponsor noted that the LUMINOUS protocol had been submitted but provided the protocol again.

(ii) The RMP provided identifies that, for all ocular safety concerns, routine pharmacovigilance will be supported by the targeted follow up of all serious post-marketing and clinical trial reported adverse events using a questionnaire/checklist. The RMP states that this is to obtain "higher quality information regarding the details of the event and to ensure a standard approach to obtain follow up information". No further

information is available on the type of information that will be collected as part of this follow-up, and therefore it is difficult to assess the contribution and appropriateness of this activity in addressing the safety concerns. Please provide further information on the details that will be collected as part of the targeted follow up.

Sponsor response

The purpose of the targeted follow up of ocular events using questionnaires and checklists is to collect event specific information (for ease of review they are attached to the response). The details in the event specific questions are supplementary to standard questions on information missing from the initial adverse event report. Information on the date of the first injection of Lucentis (treatment start date) is collected as part of the standard follow up information requested.

In addition, data on the time to onset of the event since the first injection of Lucentis (length of exposure) is included in the tables of review period cases displayed in the PSURs for all of the RMP risks, not only those with targeted checklists. Therefore, the sponsor believed that the use of the targeted checklists is appropriate and will contribute to a greater understanding of those specific events, as well as analyses of long term safety, including that beyond 3 years.

(iii) The recommended maximum dose of ranibizumab is 0.5 mg (0.05 mL) and the vial provided is intended for single use only. It is noted that in 2007 the fill volume was reduced from 0.3 to 0.23 mL, however the vial still contains enough active agent for around 4 doses. This is associated with an increased risk for overdose, transmission of infectious agents and adverse events such as increased IOP. Please comment on the fill volume of the vial, which includes approximately 4 doses, and the associated risk for overdose, transmission of infectious agents and adverse events such as increased IOP.

Sponsor response

The first Lucentis vial configuration commercialized consisted of 0.3 mL of drug product filled into a 2 cc vial. In order to reduce the risk of withdrawing two doses from one vial (resulting in a risk of overdosing and non-sterility), the fill volume was reassessed. A fill volume of 0.22 mL was shown to be the lowest satisfactory fill volume allowing a withdrawal volume of 0.055 mL with a 99.5 % confidence level. Therefore, for manufacturing purposes to ensure a minimal fill volume of 0.22 mL, a set point fill volume of 0.23 mL was chosen to take into account the accuracy of the filling pumps.

In conclusion a filling volume of 0.23mL was chosen to prevent multiple use of one vial however, still enabling to consistently withdraw the required amount of ranibizumab solution for injection for one dose.

The sponsor also noted the provision of advice in the PI.

(iv) The RMP describes the development and use of the professional and patient educational program in Europe. There is no information on the current or potential use of these programs in Australia. To assess the risk minimisation plan it is necessary to know if this activity will be used in Australia. If the educational program is intended for use in Australia, this then must be assessed for relevancy and appropriateness in Australia. Please provide further information including a justification for your intention regarding this program in Australia. Specific information on the relevance of this program in Australia, and the practical considerations here, is required. This information should consider, but not necessarily be restricted to:

- The current use of these materials in Australia,
- Any Australian input to the development or review of these products,

- If the materials are intended for use in Australia, consideration of
    - local guidelines and best practice documents regarding IVT injection technique to ensure consistency regarding advice,
    - usefulness and appropriateness in the Australian setting, and
    - monitoring the effectiveness of these materials in the Australian setting?

Sponsor response

The sponsor provided a comprehensive response to this question.

VI. Overall Conclusion and Risk/Benefit Assessment

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

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 Data

The evaluator presented the sponsor's therapeutic rationale which concluded that: "The rationale supporting the use of ranibizumab appears to be reasonably based on the current understanding of the pathophysiology of RVO and the pharmacodynamics of the drug."

The new clinical data in this submission comprised two studies that enrolled patients with visual impairment, one study in each of central retinal vein obstruction (CRVO) and branch retinal vein obstruction BRVO. These two studies also supported a population pharmacokinetic study, 09-3013. As categorised by the evaluator:

"The clinical dossier included two pivotal clinical efficacy and safety studies supporting the extension of indication to include the treatment of visual impairment due to macular oedema secondary to RVO [CRUISE and BRAVO]. CRUISE included patients with macular oedema secondary to CRVO, and BRAVO included patients with macular oedema secondary to BRVO."

Pharmacokinetics

Study 09-3013 was based on obtaining monthly samples in the first six months of BRAVO and CRUISE and as obtainable thereafter in the second six months when ranibizumab was given as needed (Table 1).

The Delegate noted that serum concentrations were low. The evaluator reported that, in the final model, creatine clearance (CrCL) was the only covariate which had a significant effect on apparent total serum clearance (CL/F), suggesting that systemic exposure to ranibizumab following monthly IVT injection regimens increases in patients with renal impairment defined by baseline CrCL. The potential for this level of renal impairment related exposure to produce ["on target"] effects mediated by VEGF inhibition was assessed to be low, "Overall, the covariate analysis demonstrated that no ranibizumab dosage adjustments based on the tested baseline patient covariates were required".

Pharmacodynamics

There were no pharmacodynamic studies in RVO. The sponsor chose the same two doses that had been used in "wet" macular degeneration, that is, 0.3 mg and 0.5 mg monthly as the doses to be used in the pivotal studies. The evaluator accepted this, accepting biological plausibility.

Efficacy

Phase III Pivotal Trials

The studies are summarised in Table 6. The worse eye was treated. The patients studied were generally elderly or very elderly and the large majority had a history of hypertension. Diabetes mellitus or glaucoma was present in a significant minority of patients. The first six months of each study was sham controlled and injections were given monthly. In the second six month period, all patients were given only active treatment as required (0.5 mg monthly if previously on sham treatment) and at monthly intervals as necessary, the latter determined by a decline in best corrected visual acuity to 20/40 (or worse) or mean central subfield thickness ≥ 250 μm on optical coherence tomography. The evaluator noted that the former re-treatment criterion is mirrored in the proposed PI but not the latter, yet the studies ran using both criteria. Both studies were randomised (1:1:1), double masked, parallel group trials with the same primary endpoint:

"The *primary objectives* of *both studies* were:

- to evaluate the efficacy of IVT injections of ranibizumab administered monthly for 6 months for the improvement of visual acuity as measured by the mean change in best corrected visual acuity (BCVA) at 6 months compared with baseline; and
- to evaluate the safety and tolerability of IVT injections of ranibizumab administered monthly for 6 months, followed by a 6 month observation period during which protocol-specified re-treatment criteria could trigger re-treatment at monthly intervals. "

There were several secondary endpoints. Enrolled patients were centrally adjudicated to determine eligibility, that is, macular oedema secondary to BRVO (for the BRAVO study), or with macular oedema secondary to CRVO (for the CRUISE study). The presence of venous obstruction was assessed by fluorescein angiography. Patients had to have been affected for no more than 12 months prior to enrolment and they had retinal vein obstruction uncomplicated by other significant ocular conditions resulting from the disease itself or other ocular diseases. This submission included 12 month data from both studies. The Delegate noted that post-injection antimicrobials were prescribed.

BRAVO (Study FVF4165g)

In this study, 82% to 83% of patients had a BRVO, and 12% to 13% of patients had a hemi-central RVO. Eighteen percent of patients had been pre-treated. In BRAVO the average number of injections received per subject (of 6 scheduled injections) was 5.5 sham injections and 5.7 ranibizumab injections for both the 0.3 mg and 0.5 mg groups.

A special feature of this study was that it included criteria for rescue treatment with laser therapy at the Month 3 visit using rescue criteria. Laser therapy was not used as a comparative treatment. Laser rescue treatment was administered to 27 (20.1%) patients in the ranibizumab 0.3 mg group, 28 (21.4%) in the ranibizumab 0.5 mg group and 76 (57.6%) in the sham group.

CRUISE (Study FVF4166g)

Fourteen percent of patients had been pre-treated. The centralised assessment found that, at baseline, 92% to 97% of the total number of patients had a CRVO (all 4 quadrants involved).

Overall, baseline visual acuity was worse in CRUISE than in BRAVO. In CRUISE the average number of injections received per subject (of 6 scheduled injections) was 5.4, 5.8 and 5.5 injections for both the 0.3 mg and 0.5 mg groups.

The primary endpoints for these studies at 6 months are shown in Table 9. All three groups improved in BRAVO but the differences for both doses of ranibizumab versus sham treatment were statistically significant and, in the opinion of the evaluator, clinically significant. The improvement in the sham group in BRAVO may be attributed in part to rescue laser treatment (57.6% of patients in the sham group) and in part the natural history of BRVO which includes spontaneous resolution in a subset of patients. As shown in the table, sham treatment showed little benefit in CRUISE.

Secondary endpoint analyses were similarly supportive of active treatment. The Delegate noted that in both studies, greater increases in visual acuity scores with both doses of ranibizumab compared with sham were observed as early as 7 days after the first treatment and were maintained throughout the 6 month treatment period.

Twelve month data

As mentioned above, all patients received active treatment as needed and the statistical analysis became descriptive. Injections were frequent in the second six month period, especially in the previously sham treated group but most patients who were given active treatment in the first 6 month period would have received 2 or 3 injections in the second six months.

As noted by the evaluator:

"In BRAVO, at Month 12 the mean changes from baseline in BCVA score (vs Month 6) for the sham, 0.3 mg and 0.5 mg groups was 12.1 (vs 7.3) letters, 16.4 (vs 16.6) letters and 18.3 (vs 18.3) letters, respectively. In CRUISE, the corresponding results were 7.3 (vs 0.8) letters, 13.9 (vs 12.7) letters and 13.9 (vs 14.9 letters). In both studies, improvement in VA scores achieved at Month 6 in both the ranibizumab groups were maintained through to Month 12, while in the sham treatment groups further improvements were observed from Month 6 through to Month 12 (see Figures 3 and 4)." This benefit was associated with repeated use of ranibizumab.

Secondary endpoints also showed a treatment effect. The evaluator concluded that improvements in the previous sham group were treatment related.

The time to onset of effect was under three months: "The results from both studies indicated that meaningful VA stability was first reached in patients in the pooled ranibizumab group at Month 3 (after the third injection)."

A retrospective review of responders to treatment in both studies suggested that:

- the response was greater in patients aged < 65 years compared with patients aged ≥ 65 years;

- a greater response was observed in subjects with better baseline visual acuity;

- a greater response was observed in patients with greater baseline central foveal thickness; and,

- the response was generally greater in patients with no prior therapy for RVO.

The evaluator supported the use of the higher dose: "While both doses of ranibizumab were efficacious, the results for the 0.5 mg dose were generally numerically superior to those for the 0.3 mg dose but the differences were relatively small. Neither of the two pivotal studies included statistical analyses of the efficacy outcomes comparing the two ranibizumab doses. It was considered that the efficacy data support the approval of the 0.5 mg dose for the treatment of patients with RVO."

Safety

The two new studies contribute safety data to 12 months. Local and non-local adverse events are shown in Table 12.

Five deaths occurred in the two studies by 12 months. No cause was given for one, the others were attributed to pneumonia, respiratory failure (n=2) and gastric cancer. Two deaths occurred in an ongoing study that has not been submitted (congestive cardiac failure, sepsis). The evaluator was of the view that the deaths cannot be causally attributed to ranibizumab but neither can they be excluded.

The evaluator concluded: "Overall, the ocular AEs reported in the study eye in patients with RVO are consistent with those previously reported for ranibizumab in patients with wet AMD and included in the currently approved Lucentis PI." Non-ocular adverse events were unremarkable in terms of new safety signals.

A number of anomalies in laboratory test results were observed by the evaluator (for example, blood glucose, raised ALT and uric acid levels and proteinuria). The Delegate noted that the evaluator reported the safety findings in detail but the overall number of serious events was small.

Evaluator's conclusions

The evaluator supported registration: "The benefit risk-balance of ranibizumab for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion is favourable for the proposed 0.5 mg dose."

Secondary Evaluation Report

This was produced in the light of the sponsor's answer to the questions raised in the List of Questions. Of these questions and answers, the following are of particular importance with respect to efficacy and dosing.

In response to the question, "Please justify why retreatment requires VA to be stable for three consecutive monthly assessments rather than requiring retreatment to continue until maximum VA is achieved and confirmed for three consecutive monthly assessments. The current retreatment recommendation has the potential to maintain VA at the level that triggered retreatment (which could be achieved after a minimum of two retreatment injections). Would it not be preferable to stop treatment altogether if no improvement has occurred after three consecutive monthly retreatment injections?", the sponsor replied:

In the situation where a retreatment does not improve the level of VA that triggered it (as in the example given in the evaluator's question), even after 2 injections (3 consecutive monthly assessments), the proposed posology recommends to stop treatment, as stability is reached and no further improvements are expected." The evaluator did not accept this answer:

"It is recommended that the section specifically state that if stable visual acuity for three consecutive monthly assessments performed while on Lucentis treatment has not been achieved then treatment with Lucentis should be discontinued. The proposed posology does not explicitly recommend that treatment stop if improvement in visual acuity has not been maintained for three consecutive visits while being treated with Lucentis."

In response to the question, "Please comment on why the decision was made not to simply adopt the dosage regimen used in the pivotal studies (initiate treatment with 6 monthly injections in all patients with subsequent retreatment then being based on loss of visual stability). The analyses supporting the proposed Dosage and Administration regimen were exploratory and were not specified or specifically tested in the pivotal studies.", the sponsor answered *inter alia*:

"The studies had a fixed monthly treatment regimen from Month 0 through Month 5 in order to allow a standardized assessment of the treatment effect at Month 6 whereas the prescribing information anticipates that in clinical practice the initial treatment phase will be tailored to the needs of the individual patient (may be longer or shorter)."

"The mean changes from baseline in the two studies show an increase in visual acuity up to Month 5 for Lucentis-treated patients with CRVO and up to Month 6 for Lucentis-treated patients with BRVO ..." and, surprisingly: *"A recommendation to treat all patients initially with 6 monthly injections as in the clinical studies (or for any other fixed period of time) would not be supported by the data."*

The time course of treatment effect is shown in Figures 3 and 4.

The evaluator has broadly accepted this. The Delegate did not. No additional study comparing a flexible versus fixed dosing regimen has been done. It was also noted that the two doses of ranibizumab produced similar results, particularly in CRVO which is more difficult to treat and for which rescue treatment was not an option.

Overall, the evaluator was of the view that the Dosage and Administration section of the PI should include an explicit statement that ranibizumab treatment be stopped if the has been no improvement at 3 consecutive visits while being treated with ranibizumab.

Risk Management Plan

As noted by the evaluator: "A number of ongoing safety concerns have been identified in the RMP, specifically 8 important identified risks (7 ocular), 7 potential risks (1 ocular), and 9 important missing information safety concerns (see Table 24)

One planned open observational study to run for 5 years that will be reported descriptively (LUMINOUS) and three ongoing studies (two in "wet" AMD and one in DME) are proposed to address all identified and potential risks, both ocular and non-ocular.

In regard to this application to register Lucentis in RVO, the evaluator commented: "Only the LUMINOUS study will enrol some patients with macular oedema secondary to RVO. However, the clinical evaluation report identifies an extension study (HORIZON, FVF3426g) which is completed but the clinical study report was not provided as part of the submission, which will provide data on the "long term persistence of treatment effect (up to 24 months)". No comment can be made on the contribution of this extension study, as it is not included in the RMP." Moreover ... ", safety data beyond 12 months in this population group is not currently available. This lack of long term safety data is reflected in the PI under Adverse Events, RVO population with a reference to "The safety of Lucentis was studied in two 12-month trials...). It is therefore recommended that a clearer statement reflecting the lack of long term safety data be considered for inclusion in the PI."

A pharmacovigilance and risk minimisation plan has been outlined for each of the ongoing safety concerns. In terms of this proposed new indication, the evaluator commented: "The PV activities in the RMP will not provide additional long term safety information specific to the current requested indication (RVO). Whether further activities are required for this indication will depend on the details of the extension study (HORIZON, FVF3426g)".

The evaluator of the RMP recommended greater transparency in the product information document in regard to the limit of evaluated experience in RVO. It was also recommended that the Horizon study be submitted for evaluation, when available.

Risk-Benefit Analysis

Delegate Considerations

Efficacy

The studies suggest that ranibizumab is of particular benefit in CRVO and suggest that monthly injections for 5 months may be not sufficient for sustained benefit. A seventh injection is commonly required and by the end of the second six month period almost all patients (95.4%) had received at least one injection those who had not (n=64 included 24 dropouts). Indeed, 18% of patients who received ranibizumab in the first six months all also received ranibizumab 12 injections in 12 months.

The opportunity cost to the patient, in terms of incomplete recovery of lost visual acuity, of switching to empirical treatment is not clear. This view is at odds with the evaluator: "It is proposed that treatment with ranibizumab 0.5 mg be interrupted once VA has been stable for the three consecutive monthly assessments. … The [sponsor's summary] included an exploratory analysis to test this proposal. In this analysis, the mean (SD) average change in VA at 1 month after an injection administered when VA stability was first achieved was +0.8 (4.6) letters in BRAVO and 1.5 (4.2) letters in CRUISE in the pooled ranibizumab groups (i.e. stability defined as VA values max – min ≤ 3 letters for 3 consecutive monthly visits with treatment at the first 2 visits). This analysis suggests that, on average, no further clinically meaningful improvement occurs in patients who have achieved stability over three consecutive monthly assessments who continue treatment". The evaluator also noted that: "Treatment decisions in individual patients relating to discontinuation for VA stability and retreatment for loss of VA stability will rest with individual clinicians as no specific VA letter criteria relating to treatment decisions have been specified in the PI."

The data do not clearly support the use of the higher dose of ranibizumab. The evaluator commented that: "Neither of the two pivotal studies included statistical analyses of the efficacy outcomes comparing the two ranibizumab doses. In general the higher dose resulted in increased efficacy, but the differences in efficacy outcomes between the two doses were small." The Delegate agreed that they are small.

A lower dose than 0.3 mg monthly has not been explored. The value of adding triamcinolone or anecortave to refractory cases/poor responders is not known but laser rescue treatment was required in about 21% of patients who received ranibizumab.

New Indication

Efficacy data are limited to 12 months.

It appears that some of the arguments received from the sponsor in regard to dosing and the dosing interval are more in the territory of pharmacoeconomics. The decision to be made will have to be based on the submitted efficacy and safety data. *Post hoc* analyses are best used for planning new studies through informing hypotheses.

The Delegate was therefore of the view that there is no basis for suggesting that 0.5 mg is the preferred dose. The PI should make it clear that both doses were clinically similar with respect to efficacy and safety. The PI should make it clear that the clinical trials are based on six doses given monthly and that it has been observed that almost all patients will require retreatment within six months of discontinuation. The sponsor was asked to comment on the completeness of recovery of visual acuity compared to best result obtained after previous treatment according to monthly therapy.

Risk Management

The Delegate supported the recommendations of the evaluator.

Proposed Actions

The Delegate proposed that the submission should be approved for the indication:

the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).

The sponsor should be encouraged to undertake clinical trials to investigate longer term response and safety.

Response from Sponsor

The sponsor welcomed the Delegate's proposal to approve the indication and addressed the specific issues raised by the Delegate. Issues relating to the PI are not included as these are beyond the scope of this AusPAR.

Horizon study

The sponsor noted that the clinical study report for the Horizon study is available and will be submitted to the TGA as a post-approval commitment.

Completeness of recovery of visual acuity

The sponsor indicated that an analysis showed that 45 (19%) of the patients who completed 12 month ranibizumab treatment in BRAVO and 14 (6%) of the patients who completed 12 month ranibizumab treatment in CRUISE did not receive any injection during the prn treatment period from Month 6 to Month 12. The completeness of recovery of VA after treatment suspension was evaluated by calculating mean changes in BCVA from baseline for the subgroup of ranibizumab treated patients in whom monthly treatment was suspended at any time from Month 6 onwards and who received re-treatment later on.

In BRAVO, 68 patients randomised to 0.3 mg and 65 patients randomised to 0.5 mg had both treatment suspension and treatment re-initiation during the "as needed" period.

In both dose groups the maximum treatment effect on VA was observed at Month 6 at which the mean changes from baseline were +20.0 letters for 0.3 mg and +19.9 letters for 0.5 mg. During the subsequent 6 months "as needed" treatment period, there were fluctuations in mean BCVA reflecting the effects of treatment suspension and treatment re-initiation. At Month 12, the mean changes from baseline were very similar to those observed at Month 6, that is, +18.7 letters in the 0.3 mg group and +19.1 letters in the 0.5 mg group.

In CRUISE, 66 patients in each of the two dose groups had both treatment suspension and treatment re-initiation during the "as needed" treatment period.

The results are generally consistent with those in BRAVO. The average treatment effect on VA increased up to Month 6 in both ranibizumab groups with fluctuations in mean BCVA occurring during the subsequent 6 month prn treatment period. At Month 6, the mean changes from baseline were +16.5 letters in patients randomised to 0.3 mg and +18.5 letters in patients randomised to 0.5 mg. Between Month 6 and Month 12, mean BCVA slightly increased to +17.2 letters in the 0.3 mg group and slightly decreased to +15.3 letters in the 0.5 mg group but these minor numerical differences between the two dose groups are unlikely to indicate a dose effect.

The fact that ranibizumab treatment effect at Month 12 was almost identical to that at Month 6 in both studies demonstrates that decreases in VA following treatment suspension can be completely offset by re-treatment in the vast majority of patients.

Indication

The sponsor proposed to slightly amend and thus clarify the wording of the indication to:

the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).

Clinical trials

The sponsor indicated that its clinical development program includes evaluation of ranibizumab treatment in patients with visual impairment due to macular oedema secondary to RVO in post-approval studies including:

- Study E2401 is evaluating efficacy and safety of the proposed treatment regimen in patients with visual impairment due to macular oedema secondary to CRVO.
- Study E2402 is evaluating efficacy and safety of the proposed treatment regimen in patients with visual impairment due to macular oedema secondary to BRVO.
- Study FVF3426g (HORIZON) is a 2 year extension study evaluating safety of Lucentis in patients with visual impairment due to macular oedema secondary to RVO.
- LUMINOUS is a global non-interventional, multicentre observational study to prospectively follow patients treated with Lucentis in real world settings. Patients will be selected for treatment based on the physician's decision to use Lucentis according to the approved indications in the label. This will include subjects with BRVO and CRVO. The objectives are to allow the capture of long term safety and efficacy data in a broad spectrum of patient experience with Lucentis treatment as well as to provide for safety data mining opportunities.

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:

Efficacy

The efficacy of ranibizumab as an IVT injection monthly in patients 18 years and over has been demonstrated. The BRAVO and CRUISE studies included sham injections and demonstrated efficacy up 12 months. The minimal duration of initial treatment is uncertain in these studies because six doses were given in both. There is no basis for suggesting that three injections will be sufficient. Moreover, a seventh or further subsequent injection was necessary in the majority of patients. It should also be noted that nearly all patients required further treatment in the second six months, although this is not reflected in the proposed regimen. These facts should be reflected in the Product Information (PI) document.

The proposed dose of 0.5 mg appears superior to the 0.3 mg dose also tested, although this was not significant.

The clinical opportunity cost to the patient of empirical treatment has not been tested. This is supported by the comments above regarding dosing schedules.

Safety

There were no new safety signals of concern noted and the number of serious adverse events was low. The committee recommended postmarket surveillance in various subgroups of patients, such as those with specific diseases or treatments (anticoagulants, steroids) which may identify patients most likely to benefit from treatment with ranibizumab.

The committee was of the view that further studies should be conducted to determine the optimum dosing interval for and duration of treatment. The sponsor was encouraged to undertake trials to study the long term effects of treatment, recognising that the potential enrolment pool of subjects eligible for such studies would be large.

The committee supported the changes to the Product Information (PI) and Consumer Medicines Information (CMI) proposed by the Delegate and evaluators and recommended the consideration of additional amendments. Discussion of such issues is beyond the scope of this AusPAR.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lucentis containing ranibizumab 1.8 mg/0.3 mL and 2.3 mg/0.23 mL solution for injection vial, indicated 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).*

Included among the specific conditions of registration was the implementation in Australia of the Lucentis (ranibizumab) Risk Management Plan (RMP), version 9, dated 8 June 2011, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

LUCENTIS®
ranibizumab (rbe)

NAME OF THE MEDICINE

Active ingredient:	Ranibizumab
Chemical name:	Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFab V2 γ1-chain), disulfide with human-mouse monoclonal rhuFab V2 κ-chain
CAS number:	347396-82-1
Molecular weight:	Approximately 48kDa
Structure:	Ranibizumab is the Fab moiety of a high affinity version of recombinant humanised monoclonal antibody rhuMAb vascular endothelial growth factor (VEGF). It consists of a 214-residue light chain linked by a disulfide bond at its C-terminus to the 231-residue N-terminal segment of the heavy chain. The expected amino acid sequences of the heavy and light chains are shown in Figures 1a and 1b.

Figure 1a The amino acid sequence of the heavy chain of ranibizumab

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         10        20        30        40        50        60
EVQLVESGGGLVQPGGSLRLSCAASGYDFTHYGMNWVRQAPGKGLEWVGWINTYTGEPTY
         70        80        90       100       110       120
AADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPYYYGTSHWYFDVWGQGTLVT
        130       140       150       160       170       180
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
        190       200       210       220       230
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHL
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Complementarity-determining regions (CDR) are underlined.

Figure 1b The amino acid sequence of the light chain of Ranibizumab

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         10        20        30        40        50        60
DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPS
         70        80        90       100       110       120
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPP
        130       140       150       160       170       180
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
        190       200       210
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
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Complementarity-determining regions (CDR) are underlined.

DESCRIPTION

Ranibizumab is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology.

Each vial contains either 1.8 mg of ranibizumab in 0.3 mL solution for intravitreal injection or 2.3 mg of ranibizumab in 0.23 mL solution for intravitreal injection. The solution is sterile, clear, colourless to pale yellow, aqueous and preservative free.

Excipients: Trehalose dihydrate, histidine hydrochloride monohydrate, histidine, polysorbate 20, water for injections.

PHARMACOLOGY

Pharmacotherapeutic group, ATC

Antineovascularisation agents, ATC code: S01LA04.

Mechanism of action

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 (e.g. $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2.

Pharmacodynamics

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 and the macular oedema causing visual impairment in diabetes and retinal vein occlusion.

Pharmacokinetics

Absorption:

Following monthly intravitreal administration of Lucentis to patients with neovascular AMD, serum concentrations of ranibizumab were generally low, with maximum levels (C_{max}) generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (11 to 27 ng/mL, as assessed in an *in vitro* cellular proliferation assay). C_{max} was dose proportional over the dose range of 0.05 to 1.0 mg/eye. Upon monthly intravitreal administration of Lucentis 0.5 mg/eye, serum ranibizumab C_{max}, attained approximately 1 day after dosing, is predicted to generally range between 0.79 and 2.90 ng/mL, and C_{min} is predicted to generally range between 0.07 and 0.49 ng/L. Serum ranibizumab concentrations in RVO patients were similar to those observed in neovascular AMD patients.

Distribution and Elimination:

Based on analysis of population pharmacokinetics and disappearance of ranibizumab from serum for patients with neovascular AMD treated with the 0.5 mg dose, the average vitreous elimination half-life of ranibizumab is approximately 9 days. Serum ranibizumab exposure is predicted to be approximately 90,000-fold lower than vitreal ranibizumab exposure.

Renal impairment: No formal studies have been conducted to examine the pharmacokinetics of Lucentis in patients with renal impairment. In a population pharmacokinetic analysis of neovascular AMD patients, 68% (136 of 200) of patients in a population pharmacokinetic analysis had renal impairment (46.5% mild [50 to 80 mL/min], 20% moderate [30 to 50 mL/min] and 1.5% severe [< 30 mL/min]). In RVO patients, 48.2% (253 of 525) had renal impairment (36.4% mild, 9.5% moderate and 2.3% severe). Systemic clearance was slightly lower, but this was not clinically significant.

Hepatic impairment: No formal studies have been conducted to examine the pharmacokinetics of Lucentis in patients with hepatic impairment.

CLINICAL TRIALS

Treatment of Wet AMD

In wet AMD, the clinical safety and efficacy of Lucentis have been assessed in three randomised, double-masked, sham**- or active-controlled studies in patients with neovascular age-related macular degeneration (AMD). A total of 1,323 patients (879 active and 444 control) was enrolled in these studies.

In study FVF2598g (MARINA), patients with minimally classic or occult with no classic choroidal neovascularisation (CNV) received monthly intravitreal injections of Lucentis 0.3 mg or 0.5 mg or sham injections. A total of 716 patients was enrolled in this study (sham, 238; Lucentis 0.3 mg, 238; Lucentis 0.5 mg, 240). A total of 664 subjects (92.7%) completed month 12 (defined as having a visual acuity score for the study eye at month 12) and a total of 615 subjects (85.9%) completed the 2-year study period. Data are available up to the end of month 24.

In study FVF2587g (ANCHOR), patients with predominantly classic CNV lesions received either: 1) monthly intravitreal injections of Lucentis 0.3 mg and sham photodynamic therapy (PDT); 2) monthly intravitreal injections of Lucentis 0.5 mg and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Sham or active verteporfin PDT was given with the initial Lucentis injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of vascular leakage. A total of 423 patients was enrolled in this study (sham, 143; Lucentis 0.3 mg, 140; Lucentis 0.5 mg, 140). A total of 386 subjects (91.3%) completed month 12 of the study and 343 subjects (81.1%) completed month 24 of the study. Data are available up to the end of month 24.

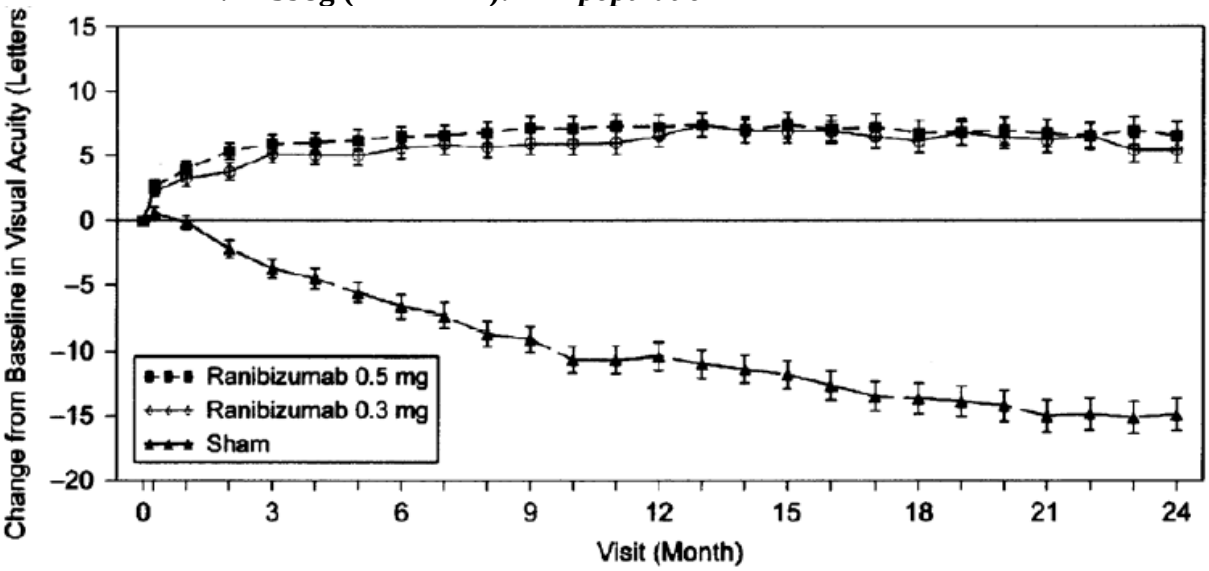
** *The sham Lucentis injection control procedure involved anesthetising the eye in a manner identical to a Lucentis intravitreal injection. The tip of a needleless syringe was then pressed against the conjunctiva and the plunger of the needleless syringe depressed.*

In both studies the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared to baseline. Almost all Lucentis-treated patients (approximately 95%) maintained their visual acuity. 34 to 40% of Lucentis-treated patients experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results.

In MARINA, the primary endpoint was fewer than 15 letters loss at 12 months. 148 of 238 randomised to sham injections met this criterion, as did 225 of 238 injected with 0.3 mg, and 227 of 240 injected with 0.5 mg. The difference between sham and injected groups is statistically ($p<0.0001$) and clinically significant but the difference between the two ranibizumab dose groups is not, as shown in Figure 2.

The visual acuity gain with ranibizumab is present at 1 month, continues to increase up to month 3, and is maintained up to month 24, compared to a gradual deterioration in the sham treatment group, as shown in Figure 2.

Figure 2 Mean change in visual acuity from baseline to month 24 in study FVF2598g (MARINA): *ITT population*



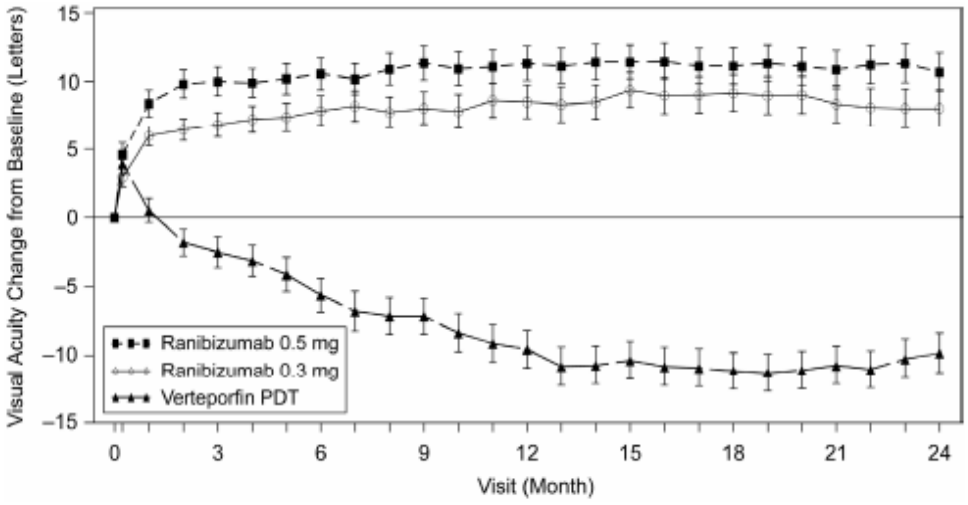
Note: The LOCF method was used to impute missing data. Vertical bars are ± 1 standard error of the mean.

In ANCHOR, the primary endpoint was fewer than 15 letters loss at 12 months. 92 of 143 randomised to sham injections and verteporfin met this criterion, as did 132 of 140 injected with 0.3 mg ranibizumab, and 134 of 140 injected with 0.5 mg.

The difference between sham and injected groups is statistically ($p<0.0001$) and clinically significant but the difference between the two doses of ranibizumab is not. The secondary endpoint of a (clinically significant) gain of at least 15 letters was met in 8 of the 143 verteporfin group and in 50 of the 140 0.3 mg group: $\chi_2= 37.6$, $p<0.0001$. 56 of the 140 0.5 mg group met this criterion also, statistically not significantly better than the 0.3 mg group: $\chi_2=0.38$, $p>0.8$.

The visual acuity gain with ranibizumab is present at 1 month, continues to increase up to month 3, and is maintained up to month 12 compared to a gradual deterioration in the verteporfin treatment group, as shown in Figure 3.

Figure 3 Mean change in visual acuity from baseline to month 24 in study FVF2587g (ANCHOR): *ITT population*



PDT = photodynamic therapy.
Note: The LOCF method was used to impute missing data. Vertical bars are ± 1 standard error of the mean.

Detailed results are shown in the tables below:

Table 1 Outcomes at month 12 and month 24 in study FVF2598g (MARINA)

Outcome measure	Month	Sham (n=238)	Lucentis 0.3 mg (n=238)	Lucentis 0.5 mg (n=240)
Loss of <15 letters in visual acuity n (%)[a] (Maintenance of vision)	Month 12	148 (62.2%)	225 (94.5%)	227 (94.6%)
	Month 24	126 (52.9%)	219 (92.0%)	216 (90.0%)
Gain of ≥15 letters in visual acuity n (%)[a]	Month 12	11 (4.6%)	59 (24.8%)	81 (33.8%)
	Month 24	9 (3.8%)	62 (26.1%)	80 (33.3%)
Mean change in visual acuity (letters) (SD)[a]	Month 12	-10.5 (16.6)	+6.5 (12.7)	+7.2 (14.4)
	Month 24	-14.9 (18.7)	+5.4 (15.2)	+6.6 (16.5)

[a] $p<0.01$.

Table 2 Outcomes at month 12 and 24 in study FVF2587g (ANCHOR)

Outcome measure	Month	Verteporfin PDT (n=143)	Lucentis 0.3 mg (n=140)	Lucentis 0.5 mg (n=140)
Loss of <15 letters in visual acuity n (%)[a] (Maintenance of vision)	Month 12	92 (64%)	132 (94%)	134 (96%)
	Month 24	94(66%)	126 (90%)	125 (90%)
Gain of ≥15 letters in visual acuity n (%)[a]	Month 12	8 (6%)	50 (36%)	56 (40%)
	Month 24	9(6%)	48 (34%)	57 (41%)
Mean change in visual acuity (letters) (SD)[a]	Month 12	-9.5 (16.4)	+8.5 (14.6)	+11.3 (14.6)
	Month 24	-9.8 (17.6)	+8.1 (16.2)	+10.7 (16.5)

[a] $p<0.01$

Patients in the group treated with Lucentis had minimal observable CNV lesion growth, on average. At month 12, the mean change in the total area of the CNV lesion was 0.1 to 0.3 DA for Lucentis versus 2.3 to 2.6 DA for the control arms.

The use of Lucentis beyond 24 months has not been studied.

In MARINA, at month 12, patients treated with Lucentis reported, on average, a statistically and clinically meaningful improvement in their ability to perform activities related to near vision, distance vision and vision-specific dependency, as measured by the NEI VFQ-25, while sham-treated patients reported a decrease in their ability to perform these activities. On the near activities scale, patients treated with 0.5 mg Lucentis reported a +10.4 point increase (0.3 mg: +9.4), while sham-treated patients had a -2.6 point decrease ($p< 0.01$). On the distance activities scale, Lucentis 0.5 mg-treated patients had a +7.0 point increase (0.3 mg: +6.7), while sham-treated patients had a -5.9 point decrease ($p< 0.01$). On the vision-specific dependency scale, Lucentis 0.5 mg-treated patients experienced +6.8 point increase (0.3 mg: +3.6), while sham-treated patients reported a decrease of -4.7 points ($p< 0.01$).

This increase from baseline in each of these three VFQ-25 subscales at month 12 was maintained at month 24 for Lucentis-treated patients, while in the sham-injection group the mean change from baseline decreased further from month 12 to month 24 in each of these subscales. Therefore, the treatment benefit of Lucentis over the sham control at month 24 was greater than that at month 12.

In ANCHOR, at month 12, patients treated with Lucentis reported a statistically and clinically meaningful improvement in their ability to perform activities related to near vision, distance vision and vision-specific dependency compared to patients receiving verteporfin PDT treatment. On the near activities scale, patients treated with 0.5 mg Lucentis reported a +9.1 point increase (0.3 mg: +6.6), while verteporfin PDT-treated patients had a +3.7 point increase ($p< 0.01$). On the distance activities scale, Lucentis 0.5 mg-treated patients reported a +9.3 point increase (0.3 mg: +6.4), while verteporfin PDT-treated patients had a

+1.7 point increase (p< 0.01). On the vision-specific dependency scale, Lucentis 0.5 mg-treated patients reported a +8.9 point increase (0.3 mg: +7.6), while verteporfin PDT-treated patients had a
-1.4 point decrease (p<0.01). In the verteporfin PDT group, the mean improvement from baseline in the near activities and distance activities subscale scores at month 12 were lost at month 24, while the mean decrease from baseline in the vision-specific dependency subscale score at month 12 was maintained at month 24. These changes between months 12 and 24 within each treatment group resulted in either maintained or greater treatment benefit of ranibizumab over verteporfin PDT compared with month 12, while the treatment benefit of ranibizumab in the vision-specific dependency subscale was smaller at month 24 compared with month 12 (p-values ranging from 0.0023 to 0.0006).

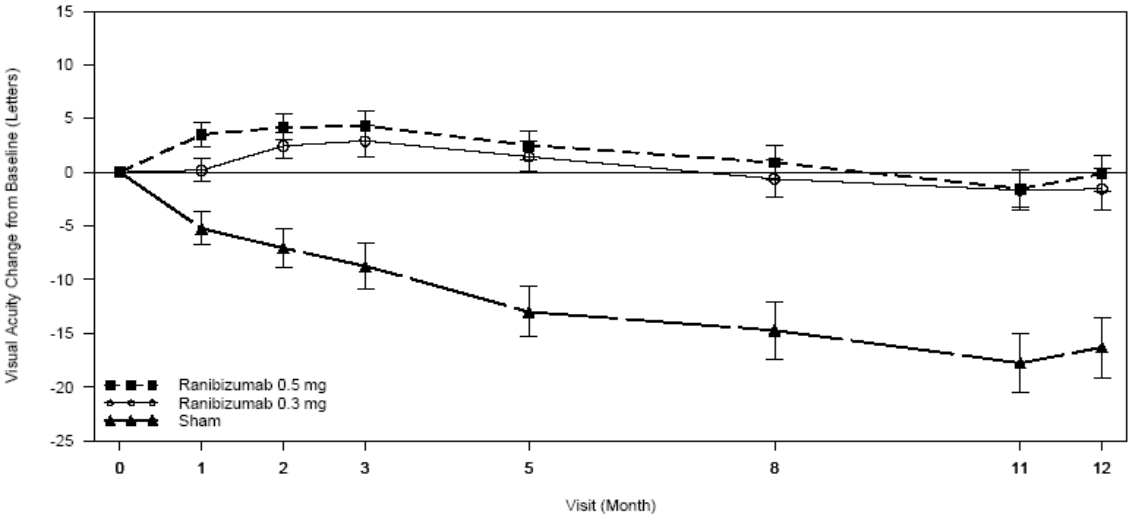
Study FVF3689g (SAILOR) was a Phase IIIb, single-masked, one-year multicentre study in naïve and previously treated subjects with CNV secondary to AMD. The primary study objective was to estimate the incidence of ocular and non-ocular serious adverse events in subjects treated for 12 months. Two thousand three hundred seventy eight patients were randomised in a 1:1 ratio to receive one intravitreal injection of 0.3 mg or 0.5 mg ranibizumab every month for three consecutive months followed by as-needed re-treatment not more often than monthly.

Overall, no imbalances between the two dose groups were observed in the frequency of ocular and non-ocular adverse events. There was a statistically non significant trend towards a higher stroke rate in the 0.5 mg group compared to the 0.3 mg group. The respective 95% CIs for the overall stroke rate were wide (0.3% to 1.3% for the 0.3 mg group vs. 0.7% to 2.0% for the 0.5 mg group). The number of strokes was small in both dose groups, and there is not sufficient evidence to conclude (or rule out) that there is a true difference in stroke rates among the treatment groups. The difference in stroke rates may be greater in patients with known risk factors for stroke, including history of prior stroke and transient ischaemic attack.

Quarterly Dosing after Three Consecutive Monthly Doses: Study FVF3192g (PIER) was a randomised, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of Lucentis in patients with neovascular AMD (with or without a classic CNV component). Data are available up to the end of month 12. Patients received Lucentis 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for three consecutive doses, followed by a dose administered once every 3 months. A total of 184 patients was enrolled in this study (Lucentis 0.3 mg, 60; Lucentis 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with Lucentis in PIER received a mean of 6 total treatments out of possible 6 from day 0 to month 12.

In PIER, the primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline (see Figure 4). After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every three months with Lucentis **lost the initial visual acuity gain**, returning to **baseline** at month 12. In PIER, almost all Lucentis-treated patients (90%) maintained their visual acuity at month 12.

Figure 4 Mean change in visual acuity from baseline to month 12 in Study FVF3192g (PIER): *ITT population*



Note: The LOCF method was used to impute missing data. Vertical bars are ±1 standard error of the mean.

Interpretation of PIER: Although less effective, treatment might be reduced to one injection every 3 months after the first three injections (e.g. if monthly injections are not feasible) but, compared to continued monthly doses, dosing every 3 months may lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following nine months. Patients should be evaluated regularly.

Treatment of Visual Impairment Due to DME

The efficacy and safety of Lucentis have been assessed in two randomized, double-masked, sham- or active controlled studies of 12 months duration in patients with visual impairment due to diabetic macular oedema. A total of 496 patients (336 active and 160 control) was enrolled in these studies, the majority had type II diabetes, 28 ranibizumab-treated patients had type I diabetes.

In study D2301 (RESTORE), a total of 345 patients with visual impairment due to macular oedema was randomised to receive either initial intravitreal injection of ranibizumab 0.5 mg as monotherapy and sham laser photocoagulation (n=116), combined ranibizumab 0.5 mg and laser photocoagulation (n=118), or sham** injection and laser photocoagulation (n=111). Treatment with ranibizumab was started with monthly intravitreal injections and continued until visual acuity was stable for at least three consecutive monthly assessments. The treatment was reinitiated when there was a reduction in best corrected visual acuity (BCVA) due to DME progression. Laser photocoagulation was administered at baseline on the same day, at least 30 minutes before injection of ranibizumab, and then as needed based on ETDRS criteria.

Key outcomes are summarised in Tables 3 and 4 and Figure 5.

Table 3 Primary Efficacy Outcomes at month 12 in study D2301 (RESTORE)

Visual acuity of the study eye (letters): Mean average change from Month 1 to Month 12 compared to baseline (Full analysis set / LOCF)

Parameter	Statistic	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
Baseline	n	115	118	110
	Mean (SD)	64.7 (10.07)	63.4 (9.99)	62.6 (11.01)
	Median	68.0	65.0	65.0
	Min - Max	38.0 - 81.0	38.0 - 79.0	36.0 - 78.0
Average Month 1 to Month 12	n	115	118	110
	Mean (SD)	70.8 (10.53)	69.2 (11.44)	63.4 (12.26)
	Median	73.7	71.5	66.2
	Min - Max	38.6 - 88.7	28.5 - 93.3	32.0 - 84.2
Average change from baseline	n	115	118	110
	Mean (SD)	6.1 (6.43)	5.9 (7.92)	0.8 (8.56)
	Median	6.1	6.0	1.3
	Min - Max	-10.9 - 25.2	-26.7 - 27.6	-37.8 - 26.8
	95% CI for mean (1)	(4.9, 7.3)	(4.4, 7.3)	(-0.8, 2.4)
Comparison vs. Laser	Difference in LS means (2)	5.4	4.9	
	95% CI for difference (2)	(3.5, 7.4)	(2.8, 7.0)	
	p-value (3)	<.0001	<.0001	

- n is the number of patients with a value for both baseline and average Month 1 to Month 12.
- Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).
- (1) Two-sided 95% confidence intervals (CI) are based on the t-distribution.
- (2) Differences in LS means and the two-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.
- (3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score

Table 4 Secondary Efficacy Outcomes at month 12 in study D2301 (RESTORE):

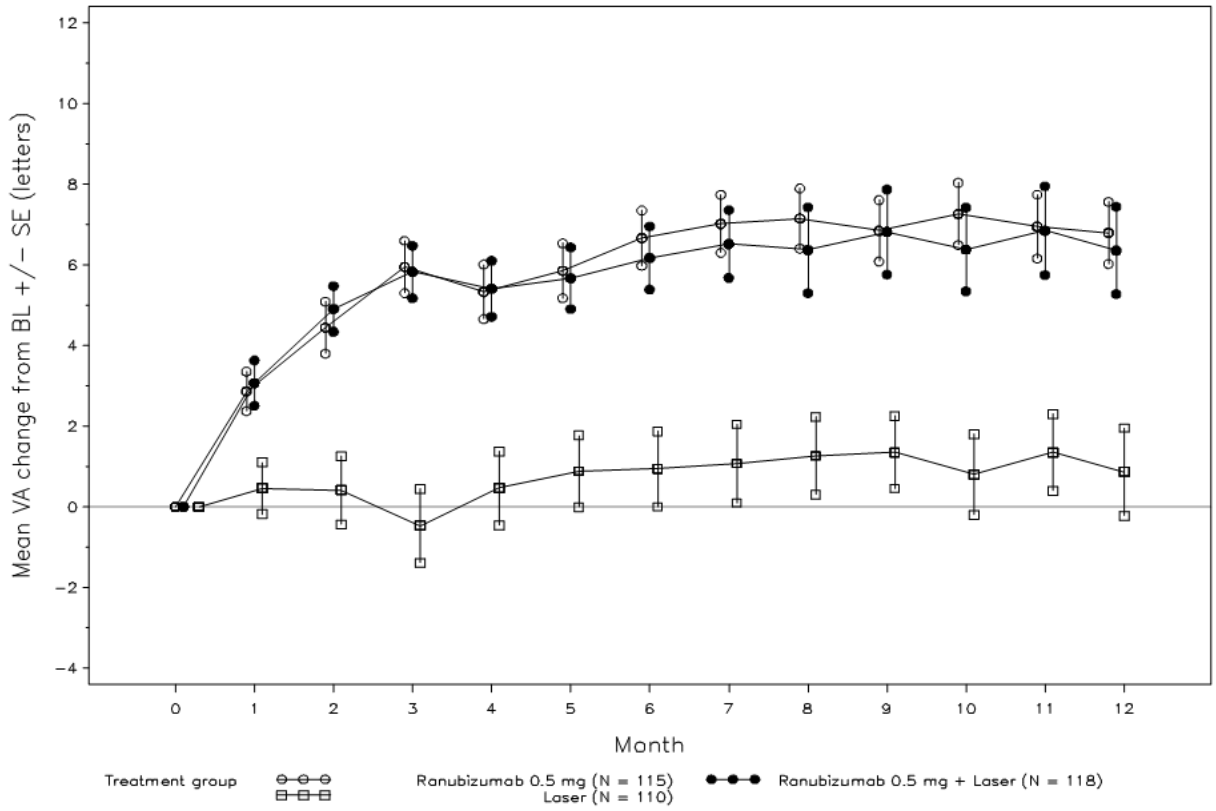
Visual acuity of the study eye (letters): Categorized change from baseline at Month 12 (FAS / LOCF)

Categorized change from baseline	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
N	115	118	110
Gain of ≥ 10 letters [1]	43 (37.4)	51 (43.2)	17 (15.5)
Loss of ≥ 10 letters	4 (3.5)	5 (4.2)	14 (12.7)
Gain of ≥ 15 letters [1]	26 (22.6)	27 (22.9)	9 (8.2)
Loss of ≥ 15 letters	1 (0.9)	4 (3.4)	9 (8.2)

- N is the number of patients with a value at both baseline and the Month 12 visit.

- [1] specified gain, or BCVA of 84 letters or more

Figure 5 Mean BCVA change from baseline over time in study D2301 (RESTORE)



In a supportive, partly exploratory study D2201 (RESOLVE), a total of 151 patients with DME with centre involvement in at least one eye, including those with focal or diffuse DME, causing visual impairment were treated with ranibizumab (6 mg/mL, n=51, 10 mg/mL, n=51) or sham (n=49) by monthly intravitreal injections until pre-defined treatment stopping criteria were met. The initial ranibizumab dose (0.3 mg or 0.5 mg) could be doubled at any time during the study after the first injection if at the Month 1 visit, retinal thickness in the study eye remained > 300 µm; or if at any monthly visit after Month 1, retinal thickness in the study eye was > 225 µm and reduction in retinal oedema from the previous assessment was < 50 µm. Laser photocoagulation rescue treatment was allowed from month 3 in both treatment arms.

The average injection doses in the 6 mg/mL group, 10 mg/mL group, and pooled group, were 0.47 mg, 0.76 mg and 0.62 mg, respectively. A total of 86% of patients in the ranibizumab treated groups received doses of 0.5 mg/injection or higher, of which 69% received doses of 0.6 mg/injection or higher.

The study was comprised of two parts: an exploratory part (the first 42 patients analysed at months 6), and a confirmatory part (the remaining 109 patients analysed at months 12).

The exploratory analysis revealed no sign of a clinically relevant response to dose doubling (in terms of efficacy neither for visual acuity nor for central retinal thickness). The results of this study therefore do not support the concept of dose doubling where response to the

recommended dose is considered inadequate. Key outcomes from the confirmatory part of the study (2/3 patients) are summarised in Tables 5 and 6 and Figure 6.

Table 5 Overall Population, VA (study eye), mean average change in letters from baseline from month 1 to month 12; FAS, LOCF of study D2201 (RESOLVE):

Visual acuity of the study eye (letters): Mean average change from baseline from Month 1 to Month 12 (Group A+B; FAS / LOCF)

Parameter	Statistic	Ranibizumab 6 mg/ml N=51	Ranibizumab 10 mg/ml N=51	Ranibizumab Pooled N=102	Sham N=49
Baseline	n	51	51	102	49
	Mean (SD)	59.2 (10.23)	61.2 (9.48)	60.2 (9.86)	61.1 (9.04)
	Median	61.0	61.0	61.0	63.0
	Min-Max	37.0-73.0	39.0-79.0	37.0-79.0	39.0-76.0
Average Month 1 to Month 12	Mean (SD)	68.4 (11.09)	67.5 (12.37)	68.0 (11.70)	61.0 (13.91)
	Median	69.4	70.4	70.3	63.0
	Min-Max	38.9-87.9	34.8-88.3	34.8-88.3	19.9-83.1
Average change from baseline	Mean (SD)	9.2 (5.60)	6.4 (9.21)	7.8 (7.72)	-0.1 (9.77)
	Median	9.5	7.4	8.2	2.8
	Min-Max	-2.9-24.3	-24.9-21.4	-24.9-24.3	-36.1-14.8
	95% CI for mean (1)	(7.7, 10.8)	(3.8, 9.0)	(6.3, 9.3)	(-2.9, 2.7)
Comparison vs. sham	Difference in LS means (2)	9.4	6.7	7.9	
	95% CI for difference (2)	(6.2, 12.6)	(3.0, 10.5)	(5.0, 10.9)	
	p-value (3)	<0.0001	0.0004	<0.0001	

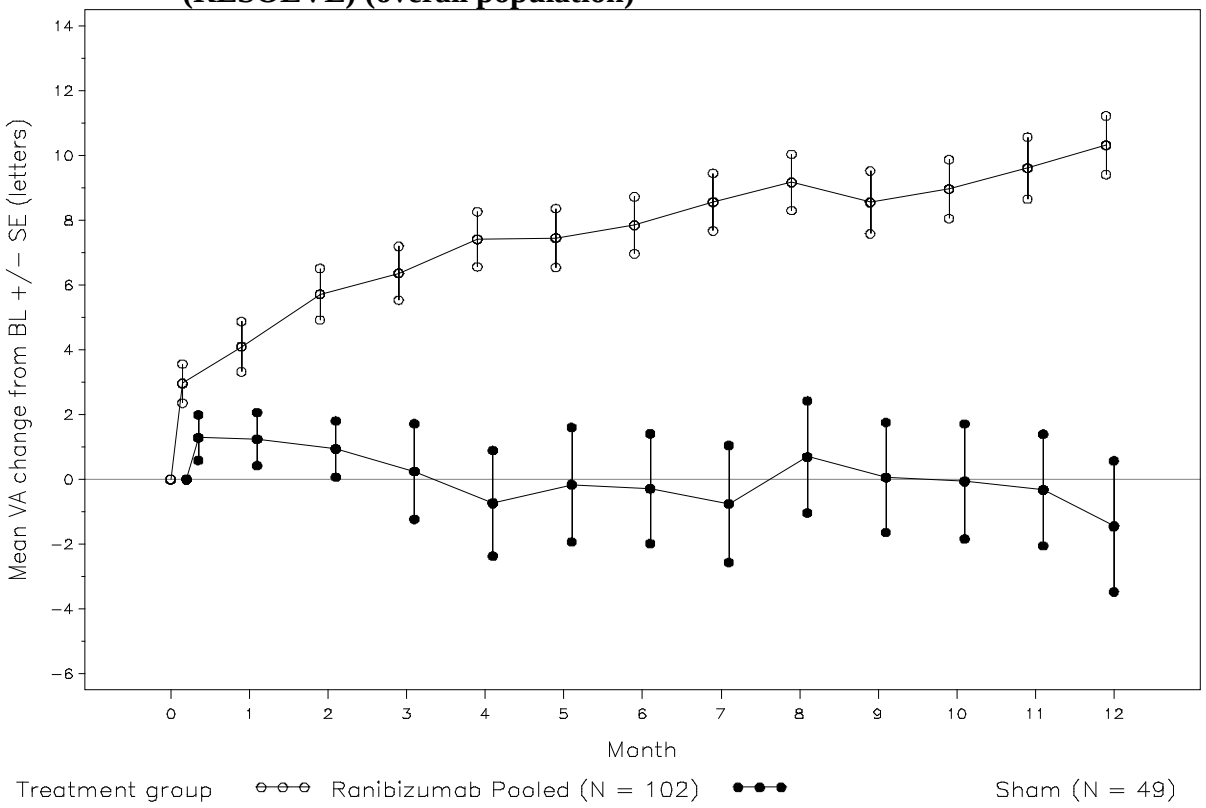
- n is the number of patients with a value for both baseline and average Month 1 to Month 12
- Stratified analysis includes baseline visual acuity (<=60, >60 letters) and baseline central retinal thickness (<=400, >400 µm).
- (1) Two-sided 95% confidence intervals (CI) are based on t-distribution.
- (2) Differences in LS means and the two-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.
- (3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score statistics.

Table 6 Overall Population, treatment comparisons key secondary efficacy variables; FAS (LOCF) of study D2201 (RESOLVE)

Variable	Ran 6mg/mL (n=51)	Ran 10mg/mL (n=51)	Ran Pooled (n=102)	Sham (n=49)
Gain ≥ 15 letters [Δ BL to month 12][1]	35.3% (n=18)	29.4% (n=15)	32.4% (n=33)	10.2% (n=5)
Loss ≥ 15 letters [Δ BL to month 12] [1]	0%	5.9% (n=3)	2.9% (n=2)	20.4% (n=10)
Gain ≥ 10 letters [Δ BL to month 12][2]	72.5% (n=37)	49.0% (n=25)	60.8% (n=62)	18.4% (n=9)
Loss ≥ 10 letters [Δ BL to month 12] [2]	0%	9.8% (n=5)	4.9% (n=5)	24.5% (n=12)
CRT μm mean (SE) [Δ BL to month 12] [3]	-200.7 (17.11)	-187.6 (20.70)	-194.2 (13.38)	-48.4 (21.92)
CRT < 225 μm (%) at month 12[4]	31.4% (n=16)	39.2% (n=20)	35.3% (n=36)	10.2% (n=5)

Δ BL = change from baseline
[1]CMH test, stratified: 6 mg/mL vs sham p=0.0001; 10 mg/mL vs sham p=0.0037; and pooled p=0.0001
[2]CMH test, stratified: 6 mg/mL vs sham p<0.0001; 10 mg/mL vs sham p=0.0010; and pooled p<0.0001
[3]CMH test, stratified: 6 mg/mL vs sham p<0.0001; 10 mg/mL vs sham p<0.0001; and pooled p<0.0001
[4]CMH test, stratified: 6 mg/mL vs sham p=0.0108; 10 mg/mL vs sham p=0.0007; and pooled p=0.0011

Figure 5 Mean change in visual acuity from baseline over time in study D2201 (RESOLVE) (overall population)



Patients treated with ranibizumab experienced a continuous reduction in central retina thickness. At month 12, the mean CRT change from baseline was -194 micrometres for ranibizumab versus -48 micrometres for sham control.

Overall, ocular and non-ocular safety findings in DME patients of both studies D2201 and D2301 were comparable with the previously known safety profile observed in wet AMD patients.

Treatment of visual impairment due to macular oedema secondary to RVO

The clinical safety and efficacy of Lucentis in patients with visual impairment due to macular oedema secondary to RVO have been assessed in the randomised, double-masked, controlled studies BRAVO and CRUISE that recruited subjects with BRVO (n=397) and CRVO (n=392), respectively. In both studies, subjects received either 0.3 mg or 0.5 mg intravitreal ranibizumab or sham** injections. Patients were initially treated monthly for 6 months. Neither study compared a flexible versus fixed dosing regimen. Thereafter, treatment was given as needed following pre-specified re-treatment criteria. After 6 months, patients in the sham-control arms were crossed over to 0.5 mg ranibizumab. In BRAVO, laser photocoagulation as rescue was allowed in all arms from Month 3.

Laser therapy was not used as a comparative treatment. During the first six months, laser rescue treatment was administered to 27 (20.1%) patients in the ranibizumab 0.3 mg group, 28 (21.4%) in the ranibizumab 0.5 mg group and 76 (57.6%) in the sham group.

In the first six months, ranibizumab was given monthly. In the second six month period, all patients were given only ranibizumab as needed i.e. were given only active treatment as required (0.5mg monthly if previously on sham treatment) and at monthly intervals as necessary, the latter determined by a best corrected visual acuity of 20/40 - or worse - or mean central subfield thickness $\geq$ 250 μm on optical coherence tomography.

Out of the 525 patients who received active treatment in the first 6 months, 501 patients entered into the observation period, with 87.2% (n=437) of them receiving at least one injection. Overall, patients received from 0 to 6 injections, with the lowest percentage of patients (10%) receiving 1 injection and the highest percentage of patients (20.8%) receiving 6 injections. The average number of injections was 3.3.

While numerically the better results were seen for 0.5 mg the differences between the two doses of Lucentis are not clinically significant. Key outcomes from BRAVO and CRUISE are summarised in Tables 7 and 8 and Figures 6 and 7.

Table 7 Outcomes at Month 6 and 12 (BRAVO)

	Sham/Lucentis 0.5 mg (n=130)	Lucentis 0.3 mg (n=134)	Lucentis 0.5 mg (n=130)
Mean change in visual acuity from baseline at Month [a] (letters) (primary endpoint)	+7.3	+16.6	+18.3
Mean change in visual acuity from baseline at Month 12 (letters)	+12.1	+16.4	+18.3
Proportion of patients gained ≥15 letters in BCVA from baseline at Month 6[a]	28.8 %	55.2%	61.1 %
Proportion of patients gained ≥15 letters in BCVA from baseline at Month 12	43.9 %	56.0%	60.3 %
Proportion of patients receiving laser rescue over 12 months	61.4 %	41.0%	34.4 %

[a] $p<0.0001$

Figure 6 Mean Change from Baseline BCVA over time to Month 6 and Month 12 (BRAVO)

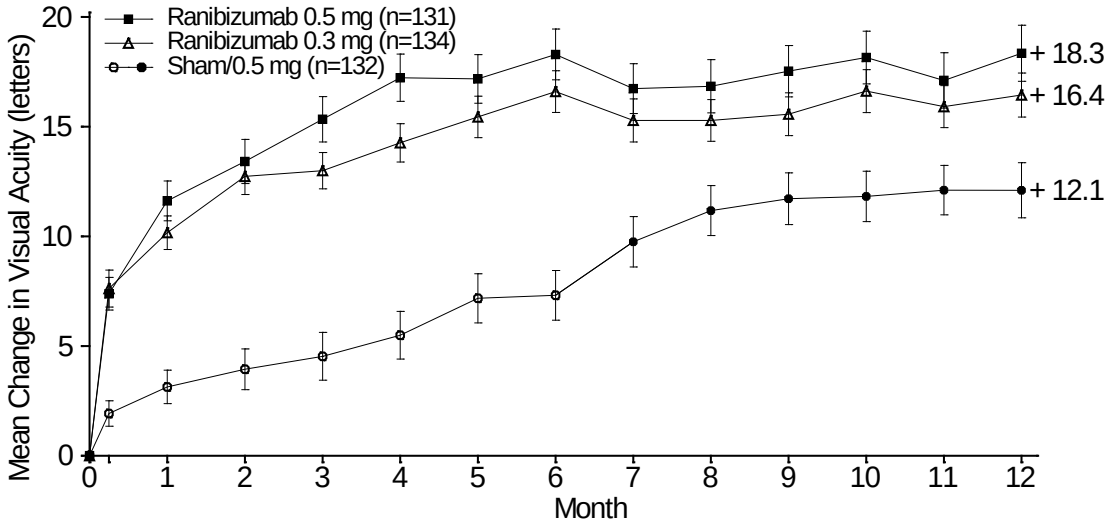
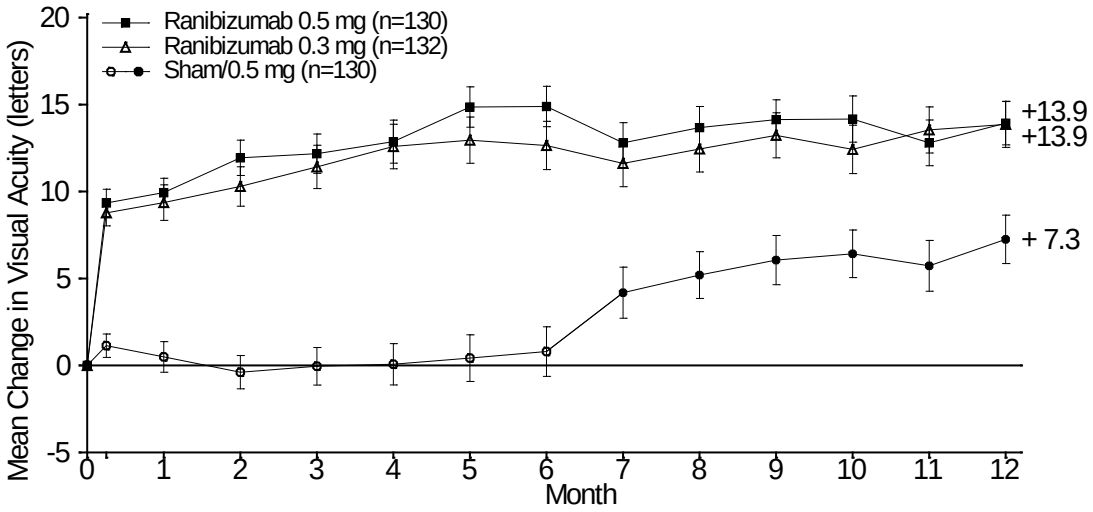


Table 8 Outcomes at Month 6 and 12 (CRUISE)

	Sham/Lucentis 0.5 mg (n=130)	Lucentis 0.3 mg (n=132)	Lucentis 0.5 mg (n=130)
Mean change in visual acuity from baseline at Month 6 (letters)[a]	+0.8	+12.7	+14.9
Mean change in visual acuity from baseline at Month 12 (letters)	+7.3	+13.9	+13.9
Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 6 [a]	16.9 %	46.2%	47.7 %
Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 12	33.1 %	47.0%	50.8 %

[a] $p<0.0001$

Figure 7 Mean Change from Baseline BCVA over time to Month 6 and Month 12 (CRUISE)



In both studies, the improvement of vision was accompanied by a continuous decrease in the macular oedema as measured by central retinal thickness.

The improvement in visual acuity seen with ranibizumab treatment at 6 and 12 months was

accompanied by patient-reported benefits as measured by the National Eye Institute Visual Function Questionnaire (VFQ-25) sub-scales related to near and distance activity, a pre-specified secondary efficacy endpoint. The difference between Lucentis 0.5 mg and the control group was assessed at Month 6 with p-values of 0.02 to 0.0002.

Efficacy and safety of Lucentis for treatment of visual impairment due to macular oedema secondary to RVO has not been evaluated beyond 12 months.

INDICATIONS

Lucentis (ranibizumab) is indicated 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).

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with active or suspected ocular or periocular infections.
- Patients with active intraocular inflammation.

PRECAUTIONS

Intravitreal injections, including those with Lucentis, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear, iatrogenic traumatic cataract and increased intraocular pressure (see **ADVERSE EFFECTS**). Symptoms of these adverse effects should be explained and the patient should be given a copy of the consumer medicine information document. The patient should be given contact details in the case of adverse effects.

Proper aseptic injection techniques must always be used when administering Lucentis. In addition, patients should be reviewed during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above-mentioned events without delay.

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Lucentis (see **ADVERSE EFFECTS**). Sustained IOP increases have also been reported but the frequency is unclear. Both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately. Patients should be reviewed for IOP rise pre-injection and 60 minutes post-injection.

The safety and efficacy of Lucentis therapy administered to both eyes concurrently have not been studied (see **DOSAGE AND ADMINISTRATION**).

There is a potential risk of arterial thromboembolic events following intravitreal use of inhibitors of VEGF. In the wet AMD Phase III studies, the overall frequency of arterial thromboembolic events was similar between ranibizumab and control. A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5 mg compared to ranibizumab 0.3 mg or control, however, the differences were not statistically significant. The difference in stroke rates may be greater in patients with known risk factors for stroke, including history of prior stroke or transient ischemic attack. Therefore, these patients should be carefully evaluated by their physicians as to whether Lucentis treatment is appropriate and the benefit outweighs the potential risk.

As with all therapeutic proteins, there is a potential for immunogenicity with Lucentis.

There is only limited experience in the treatment of subjects with DME due to type I diabetes. Lucentis has not been studied in patients who have previously received intravitreal injections, in patients with active systemic infections, proliferative diabetic retinopathy, or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Lucentis in diabetic patients with an HbA1c over 12% and uncontrolled hypertension.

There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischemic branch RVO (BRVO) and central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischemic visual function loss, treatment is not recommended.

Effects on Fertility

No study has been conducted to investigate the effects of ranibizumab on male or female fertility. In animal studies with bevacizumab, a closely related recombinant anti-VEGF monoclonal antibody, a reversible inhibition of ovarian function was observed in rabbits and cynomolgus monkeys following intravenous treatment. This finding is thought to be associated with inhibitory effects of bevacizumab on angiogenesis. The clinical relevance of this finding to Lucentis is unclear.

Use in Pregnancy (Category D)

For ranibizumab, no clinical data on exposed pregnancies are available. The potential risk for humans is unknown.

In pregnant monkeys, intravitreal ranibizumab treatment did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta, at doses up to 1 mg/eye/fortnight, yielding systemic exposure levels estimated to be up to 58-times those expected clinically. However, based on its pharmacological effect ranibizumab should be regarded as potentially teratogenic and embryo-foetotoxic. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

The absence of ranibizumab-mediated effects on the embryo-foetal development is plausibly related to the expected inability of the Fab fragment to cross the placenta. Nevertheless, ranibizumab was detected in a foetus coincident with high maternal ranibizumab and anti-ranibizumab antibody serum levels, possibly because the anti-ranibizumab antibody acted as a (Fc region containing) carrier protein for ranibizumab, thereby decreasing its maternal serum clearance and enabling its placental transfer.

As the embryo-foetal development investigations were performed in healthy pregnant animals and disease (e.g. diabetes) may modify the permeability of the placenta towards a Fab fragment, ranibizumab should be used with caution in women of child bearing potential in general, and during pregnancy in particular.

Women of Childbearing Potential

Women of childbearing potential should use effective contraception during treatment (see **PRECAUTIONS Use in Pregnancy**).

Use in Lactation

It is not known whether ranibizumab is excreted in human milk. As a precautionary measure, breast-feeding is not recommended during the use of Lucentis.

Children and Adolescents (below 18 years of age)

Safety and efficacy of Lucentis have not been tested in children and adolescents below 18 years of age. Lucentis is therefore not recommended for use in these sub-populations.

Elderly (65 years and above)

No dose adjustment is required in the elderly.

Hepatic Impairment

Lucentis has not been studied in patients with hepatic impairment. However, as systemic exposure is negligible, no special measures are considered necessary in this population.

Renal Impairment:

Dose adjustment is not needed in patients with renal impairment (see **PHARMACOLOGY Pharmacokinetics**).

Carcinogenicity

No carcinogenicity studies were performed with ranibizumab.

Genotoxicity

No genotoxicity studies were performed with ranibizumab.

Interactions with Other Drugs

No formal interaction studies have been performed (see **CLINICAL TRIALS**).

For the adjunctive use of verteporfin and Lucentis in wet AMD, see **CLINICAL TRIALS**.

For the adjunctive use of laser photocoagulation and Lucentis in DME and BRVO, see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**.

Effects on Ability to Drive and Use Machines

The Lucentis treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines (see **ADVERSE EFFECTS**). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

ADVERSE EFFECTS

Wet AMD Population

A total of 1,315 patients constituted the safety population in the three phase III studies in wet AMD with 24 months exposure to Lucentis and 440 patients were treated with the 0.5mg dose.

Serious adverse events related to the injection procedure included endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see **PRECAUTIONS**). The cumulative 2-year incidence of endophthalmitis (serious and non-serious) in the pooled pivotal trials (i.e. studies FVF2598g(MARINA), FVF2587g (ANCHOR), and FVF3192g (PIER)) was about 1%.

Other serious ocular events observed among Lucentis-treated patients included intraocular inflammation and increased intraocular pressure (see **PRECAUTIONS**).

The adverse events listed below occurred at a higher rate (at least 2 percentage points) in patients receiving treatment with Lucentis 0.5 mg than in those receiving control treatment (sham injection (see definition under **CLINICAL TRIALS**) or verteporfin photodynamic therapy (PDT)) in the pooled data of the three controlled wet AMD phase III studies FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER). They were therefore considered potential adverse drug reactions. The safety data described below also include all adverse events suspected to be at least potentially related to the injection procedure or medicinal product in the 440 patients of the combined 0.5 mg treatment groups in wet AMD. The adverse event rates for the 0.3 mg dose were comparable to those for 0.5 mg.

DME population

The safety of Lucentis was studied in a one-year sham-controlled trial (RESOLVE) and in a one-year laser-controlled trial (RESTORE) conducted respectively in 102 and 235 ranibizumab-treated patients with visual impairment due to DME (see **CLINICAL TRIALS**).

The event of urinary tract infection, in the common frequency category, met the criteria for the table above; otherwise ocular and non-ocular events in the RESOLVE and RESTORE

trials were reported with a frequency and severity similar to those seen in the wet AMD trials.

Post-Registration Study in DME population

An analysis of 24-month data from two Phase III studies in DME, RIDE and RISE, is available. Both studies are randomised, sham-controlled studies of monthly intravitreal ranibizumab injections (0.5 mg or 0.3 mg) for a total of 36 months in patients with clinically significant macular oedema with centre involvement secondary to diabetes mellitus (type 1 or type 2). The patients are treated using a fixed dosing regimen which requires monthly injections as opposed to the approved individualised dosing regimen (see **DOSAGE AND ADMINISTRATION**). A total of 500 patients were exposed to ranibizumab treatment in the pooled studies (250 patients in each pooled ranibizumab 0.3mg and 0.5mg arm as well as the sham arm.

The pooled safety analysis showed a numerically higher, but not statistically significant, number of deaths and cerebrovascular events in the 0.5mg group as compared to the 0.3mg or sham groups. The stroke rate at 2 years was 3.2% (8/250) with 0.5mg ranibizumab, 1.2% (3/250) with 0.3mg ranibizumab, and 1.6% (4/250) with sham. Fatalities in the first 2 years occurred in 4.4% (11/250) of patients treated with 0.5mg ranibizumab, in 2.8% (7/250) treated with 0.3mg ranibizumab, and in 1.2% (3/250) of control patients.

RVO population

The safety of Lucentis was studied in two 12-month trials (BRAVO and CRUISE) conducted respectively in 264 and 261 ranibizumab-treated patients with visual impairment due to macular oedema secondary to Branch RVO (BRVO) and Central RVO (CRVO), respectively (see **CLINICAL TRIALS**). Ocular and non-ocular events in the BRAVO and CRUISE trials were reported with a frequency and severity similar to those seen in the wet-AMD trials.

Tabulated summary of adverse effects from clinical trials

The adverse effects from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse effects are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS): very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Table 7 Adverse Effects from Clinical Trials

Infections and Infestations	
Very common	Nasopharyngitis
Common	Influenza, urinary tract infection*
Blood and lymphatic system disorders	
Common	Anaemia
Psychiatric disorders	
Common	Anxiety
Nervous system disorders	
Very common	Headache
Common	Stroke
Eye disorders	
Very common	Intraocular inflammation, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritis.
Common	Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia.
Uncommon	Blindness, endophthalmitis, hypopyon, hyphaema, keratopathy, iris adhesions, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation.
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Gastrointestinal disorders	
Common	Nausea
Skin and subcutaneous tissue disorders	
Common	Allergic reactions (rash, urticaria, pruritis, erythema)
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Investigations	
Very common	Intraocular pressure increase

*Observed only in the DME population

DOSAGE AND ADMINISTRATION

Single-use vial for intravitreal use only. Use of more than one injection from a vial can lead to contamination and subsequent infection.

Lucentis must be administered by a qualified ophthalmologist experienced in intravitreal injections.

The recommended maximal dose (0.5 mg) should not be exceeded. One eye only should be injected on each occasion and post-injection monitoring is recommended (see **PRECAUTIONS**).

Treatment of Wet AMD

The recommended dose of Lucentis is 0.5 mg (0.05 mL) or 0.3 mg (0.03 mL) given as a single intravitreal injection.

Lucentis is given monthly. The interval between two doses should not be shorter than 1 month. Although less effective, treatment might be reduced to one injection every 3 months after the first three injections (e.g. if monthly injections are not feasible) but, compared to continued monthly doses, dosing every 3 months may lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following nine months. Patients should be evaluated regularly.

Treatment of Visual Impairment due to DME

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

Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to DME and continued until stable visual acuity is reached again for three consecutive monthly assessments. The interval between two doses should not be shorter than one month.

Lucentis and Laser Photocoagulation in DME

Lucentis has been used concomitantly with laser photocoagulation in clinical trials (see **CLINICAL TRIALS**). When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation. Lucentis can be administered in patients who have received previous laser photocoagulation.

Treatment of visual impairment due to macular oedema secondary to RVO

The recommended dose of Lucentis is 0.5 mg (0.05 mL) or 0.3 mg (0.03 mL) given as a single intravitreal injection. The interval between two doses should not be shorter than one month.

Treatment is given monthly for six months. Consideration should be given to ceasing treatment if no response is seen after 3-4 injections.

Thereafter, treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to macular oedema secondary to RVO and continued until stable visual acuity is reached for three consecutive monthly assessments. Experience in the clinical trials regarding individual needs during the second 6-month period shows a wide variation in the number of injections required (see CLINICAL TRIALS). Evaluated experience beyond a total of 12 months and a maximum of 12 injections is not available.

Lucentis and laser photocoagulation in Branch RVO (BRVO): Lucentis has been used concomitantly with laser photocoagulation in clinical studies (see **CLINICAL TRIALS**). When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation. Lucentis can be administered in patients who have received previous laser photocoagulation.

Mode of Administration

As with all medicinal products for parenteral use, Lucentis should be inspected visually for particulate matter and discolouration prior to administration.

The injection procedure should be carried out under aseptic conditions, which include the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent), and the availability of sterile paracentesis (if required). The patient's medical history should be carefully evaluated for hypersensitivity reactions prior to performing the intravitreal procedure (see **CONTRAINDICATIONS**). The periocular skin, eyelid and ocular surface should be disinfected. Adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection.

The patient should be instructed to self-administer antimicrobial drops four times daily for 3 days before and after each injection. Current practice guidelines should be considered when prescribing antibiotics.

For information on preparation of Lucentis, see **Instructions for Use and Handling**.

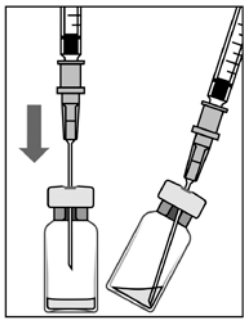
The injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 mL or 0.03 mL is then delivered; the scleral site should be rotated for subsequent injections.

Instructions for Use and Handling

Vials are for single use only.

To prepare Lucentis for intravitreal injection, please adhere to the following instructions:

A.

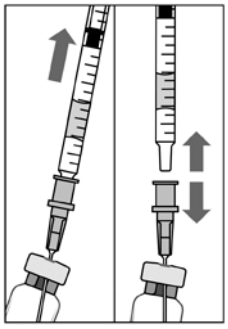


1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.

2. Assemble the 5 µm filter needle (provided) onto the 1 mL syringe (provided) using aseptic technique. Push the blunt filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial.

3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.

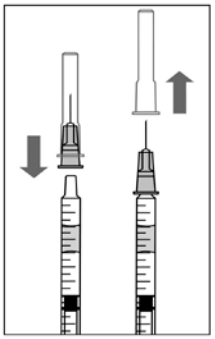
B.



4. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

5. Leave the blunt filter needle in the vial and disconnect the syringe from the blunt filter needle. The filter needle should be discarded after withdrawal of the vial contents and should not be used for the intravitreal injection.

C.

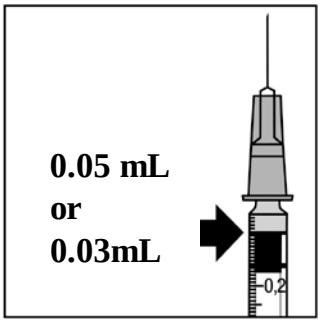


6. Aseptically and firmly assemble the injection needle (provided) onto the syringe.

7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe.

Note: Grip at the yellow hub of the injection needle while removing the cap.

D.



8. Carefully expel the air from the syringe and adjust the dose to the 0.05 mL or 0.03mL mark on the syringe. The syringe is ready for injection.

Note**:** Do not wipe the injection needle. Do not pull back on the plunger.

Any unused product or waste material should be disposed of in accordance with local requirements.

Lucentis contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Incompatibilities: In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Storage: Store at 2°C to 8°C (refrigerate - do not freeze). Protect from light.

Keep the vial in the outer carton in order to protect from light.

OVERDOSAGE

Cases of accidental overdose have been reported from the clinical studies in wet AMD and post-marketing data. Adverse reactions most frequently associated with these reported cases were intraocular pressure increased and eye pain. If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION

Lucentis is supplied as 0.23 mL or 0.3 mL solution for injection in glass vials (colourless type I glass) with chlorobutyl rubber stopper. One pack contains one vial, one filter needle for withdrawal of the vial contents, one needle for intravitreal injection and one syringe for withdrawal of the vial contents and for intravitreal injection. Each 0.23 mL vial contains 2.3 mg and each 0.3mL vial contains 1.8 mg of ranibizumab.

Poisons Schedule: Schedule 4.

SPONSOR

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Reference/Publication #